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Glycinamide derivatives

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Glycinamide derivatives

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Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the p21^{ras}/raf pathway.

The p21^{ras} gene was discovered as an oncogene of the Harvey (rasH) and Kirsten (rasK) rat sarcoma viruses. In humans, characteristic mutations in the cellular ras gene (c-ras) have been associated with many different types of cancers. These mutant alleles, which render Ras constitutively active, have been shown to transform cells, such as the murine cell line NIH 3T3, in culture.

The p21^{ras} oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30 % of all human cancers (Bolton et al. (1994) Ann. Rep. Med. Chem., 29, 165-74; Bos. (1989) Cancer Res., 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction cascade directed by growth factor receptors in almost all tissues (Avruch et al. (1994) Trends Biochem. Sci., 19, 279-83).

Biochemically, ras is a guanine nucleotide binding protein, and cycling between a GTP-bound activated and a GDP-bound resting form is strictly controlled by ras endogenous GTPase activity and other regulatory proteins. The ras gene product binds to guanine triphosphate (GTP) and guanine diphosphate (GDP) and hydrolyzes GTP to GDP. It is the GTP-bound state of Ras that is active. In the ras mutants in cancer cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells which carry these mutants (Magnuson et al. (1994) Semin. Cancer Biol., 5, 247-53). The ras proto-oncogene requires a functionally intact raf-1 proto-oncogene in order to transduce growth and differentiation signals initiated by receptor and non-receptor tyrosine kinases in higher eukaryotes.

Activated Ras is necessary for the activation of the c-raf-1 proto-oncogene, but the biochemical steps through which Ras activates the Raf-1 protein (Ser/Thr) kinase are now well characterized. It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK also called ERK, the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype see: Daum et al. (1994) Trends Biochem. Sci., 19, 474-80; Fridman et al. (1994) J Biol. Chem., 269, 30105-8. Kolch et al. (1991) Nature, 349, 426-28) and for review Weinstein-Oppenheim et al. Pharm. & Therap. (2000), 88, 229-279.

Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., Nat. Med. 1996, 2, 668-75).

Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al. (1988) in The oncogene handbook; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184; Rapp, U.R., et al. (1990) Inv Curr. Top. Microbiol. Immunol. Potter and Melchers (eds), Berlin, Springer-Verlag 166:129-139).

Three isozymes have been characterized:

c-Raf (Raf-1) (Bonner, T.I., et al. (1986) Nucleic Acids Res. 14:1009-1015). A-Raf (Beck, T.W., et al. (1987) Nucleic Acids Res. 15:595-609), and B-Raf (Qkawa, S., et al. (1998) Mol. Cell. Biol. 8:2651-2654; Sithanandam, G. et al. (1990) Oncogene:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) Oncogene 5:345-351).

Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase

by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) *Mol. Cell. Biol.* 10:2503-2512; Rapp, U.R., et al. (1987) in *Oncogenes and cancer* S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific Press, Tokyo). Microinjection into NIH 3T3 cells of
5 oncogenically activated but not wild-type versions of the Raf-protein prepared with *Escherichia coli* expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in *Oncogenes and cancer*; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo;
10 Smith, M. R., et al (1990) *Mol. Cell. Biol.* 10:3828-3833).

Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase is a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from
15 a block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in *The Oncogene Handbook*, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) *Nature (London)* 320:540-543).

20 c-Raf function is required for transformation by a variety of membrane-bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) *Nature (London)* 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation
25 (Morrison, D.K., et al. (1989) *Cell* 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) *Exp. Brain Res.* 84:403; Rapp, U.R., et al. (1988) *Cold Spring Harbor Sym. Quant. Biol.* 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:8855-8859),
30 colony-stimulating factor (Baccarini, M., et al. (1990) *EMBO J.* 9:3649-3657), insulin (Blackshear, P.J., et al. (1990) *J. Biol. Chem.* 265:12115-12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) *Proc. Natl. Acad. Sci. USA* 88:1227), and interleukin 3 and
35

granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

5 Upon mitogen treatment of cells, the transiently activated Raf-1 protein serine kinase translocates to the perinuclear area and the nucleus (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184). Cells containing activated Raf are altered in their pattern of gene expression (Heidecker, G., et al. (1989) in Genes and signal transduction in multistage carcinogenesis, N. Colburn (ed.), Marcel Dekker, Inc., New York, pp. 339-374), and Raf
10 oncogenes activate transcription from Ap-1/PEA3-dependent promoters in transient transfection assays (Jamal, S., et al (1990) Science 344:463-466; Kaibuchi, K., et al (1989) J. Biol. Chem. 264:20855-20858; Wasylyk, C., et al. (1989) Mol. Cell. Biol. 9:2247-2250).

15 There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (KC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12131-12134; Kovacina, K.S., et al (1990) J. Biol. Chem. 265:12115-12118; Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA
20 85:8855-8859; Siegel, J.N., et al (1990) J. Biol. Chem. 265:18472-18480; Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by autophosphorylation or may be caused entirely by autophosphorylation
25 initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) Science 233:305-312).

30 The present invention provides compounds generally described as glycineamides, including both aryl and/or heteroaryl derivatives which are preferably inhibits the enzyme raf kinase. Since the enzyme is a downstream effector of p21^{ras}, the inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell
35 growth mediated by raf kinase. In particular, the compounds are useful in

the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compound of Formula I or a pharmaceutically acceptable salt thereof is administered for the treatment of diseases mediated by the raf kinase pathway especially cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds are useful in the treatment of complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus type1) induced immunodeficiency (Popik et al. (1998) J Virol, 72: 6406-6413).

Therefore, subject of the present invention are glycinamide derivatives of formula I

A-D-B

(I)

wherein

D is a bivalent glycinamide moiety which is bonded to A and B, preferably via its N, N'-atoms,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-L-(M-L')_{\alpha}$, where L is a 5, 6 or 7 membered cyclic structure, preferably selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, preferably selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least to one atom, α is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L' is preferably

substituted by at least one substituent selected from the group consisting of $-\text{SO}_\beta\text{R}_x-\text{C}(\text{O})\text{R}_x$ and $-\text{C}(\text{NR}_y)\text{R}_z$

- 5 B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms, preferably of up to 20 carbon atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, preferably a 5- or 6-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is preferably selected from the group consisting of aryl, heteroaryl and heterocyclyl, R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,
- 10
- 15 R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;
- 20
- R_x is R_z or NR_aR_b , where R_a and R_b are
- 25 a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms, selected from N, S and O, and are optionally substituted by halogen, or
- 30 $-\text{OSi}(\text{R}_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, and
- 35 are optionally substituted by halogen;

or

- b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based I substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or
- c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo and W_γ , where γ is 0-3; wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen; wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_\beta$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_{\beta-}$, $-(CH_2)_\beta S-$, $-(CH_2)_\beta N(R^7)-$, $-O(CH_2)_\beta-CHHal-$, $-CHAl_2-$, $-S-(CH_2)-$ and $-N(R^7)(CH_2)_\beta-$ where $\beta = 1-3$, and Hal is halogen;

and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to perhalo, and optionally substituted by $Z_{\delta 1}$ wherein $\delta 1$ is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, A and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and with R⁷ as defined above.

More preferred, in the compound of formula I,

R_y is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C₇₋₂₄ alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₄ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ alkaryl or substituted C₇₋₂₄ aralkyl, where R_y is a substituted group, it is substituted by halogen up to per halo,

R_z is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from S, N and O, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, substituted C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from S, N and O, substituted C₇₋₂₄ alkaryl or substituted C₇₋₂₄ aralkyl where R_z is a substituted group, it is substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂

aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C₃₋₁₂ hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,

R_a and R_b are,

- 10 a) independently hydrogen, a carbon based moiety selected from the group consisting of C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O,
- 15 C₇₋₂₄ aralkyl, C₇₋₂₄ alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₂ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo heteraryl, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g; or
- 25 -OSi(R_f)₃ where R_f is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O,
- 30 C₇₋₂₄ aralkyl, C₇₋₂₄ alkaryl, substituted C₁₋₁₀ alkyl, substituted
- 35

5 C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₂ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_{3-C12} hetaryl up to per halo heteraryl, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g,

15

or

- 20 b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C_{1-C10} alkyl, C_{1-C10} alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C_{7-C24} alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₂ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo
- 25
- 30
- 35 c)

substituted aryl up to per halo aryl, C₃-C₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃-C₁₂ hetaryl up to per halo heteraryl, halo substituted C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,

or

- d) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆-C₁₂ halo substituted aryl up to per halo aryl, C₃-C₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃-C₁₂ hetaryl up to per halo heteraryl, halo substituted C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,
 where R_g is C₁₋₁₀ alkyl; -CN, -CO₂R_d, -OR_d, -SR_d, -NO₂, -C(O)R_e, -NR_dR_e, -NR_dC(O)OR_e and -NR_d(CO)R_e and R_d and R_e are independently selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆₋₁₂ aryl, C₃-C₁₂ hetaryl with 1-3 heteroatoms selected from O, N and S and C₇-C₂₄ aralkyl, C₇-C₂₄ alkaryl, up to per halo substituted C₁-C₁₀ alkyl, up to per halo substituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C₆-C₁₄ aryl, up to per halo substituted C₃-C₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and up to per halo substituted C₇-C₂₄ aralkyl,

- W is independently selected from the group consisting $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_1\text{-C}_{10}$ alkenoyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl having 0-3 heteroatoms selected from O, S and N, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_7\text{-C}_{24}$ aralkyl, $\text{C}_3\text{-C}_{12}$ heteroaryl having 1-3 heteroatoms selected from O, N and S, $\text{C}_4\text{-C}_{23}$ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted $\text{C}_1\text{-C}_{10}$ alkoxy, substituted $\text{C}_2\text{-C}_{10}$ alkenyl, substituted $\text{C}_1\text{-C}_{10}$ alkenoyl, substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted $\text{C}_6\text{-C}_{12}$ aryl, substituted $\text{C}_3\text{-C}_{12}$ hetaryl having 1-3 heteroatoms selected from O, N and S, substituted $\text{C}_7\text{-C}_{24}$ aralkyl, substituted $\text{C}_7\text{-C}_{24}$ alkaryl, substituted $\text{C}_4\text{-C}_{23}$ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and $-\text{Q-Ar}$;
- R^7 is independently selected from H, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_1\text{-C}_{10}$ alkenoyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl having 0-3 heteroatoms selected from O, C and N, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_3\text{-C}_{13}$ hetaryl having 1-3 heteroatoms selected from O, N and S, $\text{C}_7\text{-C}_{14}$ alkaryl, $\text{C}_7\text{-C}_{24}$ aralkyl, $\text{C}_4\text{-C}_{23}$ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted $\text{C}_1\text{-C}_{10}$ alkyl, up to per-halosubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per-halosubstituted $\text{C}_6\text{-C}_{14}$ aryl, up to per-halosubstituted $\text{C}_3\text{-C}_{13}$ hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted $\text{C}_7\text{-C}_{24}$ aralkyl, up to per-halosubstituted $\text{C}_7\text{-C}_{24}$ alkaryl, and up to per-halosubstituted $\text{C}_4\text{-C}_{23}$ alkheteroaryl; and each
- Z is independently selected from the group consisting $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_1\text{-C}_{10}$ alkenoyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl having 0-3 heteroatoms selected from O, S and N, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_7\text{-C}_{24}$ aralkyl, $\text{C}_3\text{-C}_{12}$ heteroaryl having 1-3 heteroatoms selected from O, N and S, $\text{C}_4\text{-C}_{23}$ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted $\text{C}_1\text{-C}_{10}$ alkoxy, substituted

C₂-C₁₀ alkenyl, substituted C₁-C₁₀ alkenoyl, substituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C₆-C₁₂ aryl, substituted C₃-C₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷.

According to the invention, each M independently from one another represents a bond OR is a bridging group, selected from the group consisting of (CR⁷R⁷)_h, or (CHR⁷)_h-Q-(CHR⁷)_i, wherein

Q is selected from a group consisting of O, S, N-R⁷, (CHal₂)_j, (O-CHR⁷)_j, (CHR⁷-O)_j, CR⁷=CR⁷, (O-CHR⁷CHR⁷)_j, (CHR⁷CHR⁷-O)_j, C=O, C=S, C=NR⁷, CH(OR⁷), C(OR⁷)(OR⁷), C(=O)O, OC(=O), OC(=O)O, C(=O)N(R⁷), N(R⁷)C(=O), OC(=O)N(R⁷), N(R⁷)C(=O)O, CH=N-O, CH=N-NR⁷, OC(O)NR⁷, NR⁷C(O)O, S=O, SO₂, SO₂NR⁷ and NR⁷SO₂, wherein

R⁷ is in each case independently selected from the meanings given above, preferably from hydrogen, halogen, alkyl, aryl, aralkyl,

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2, or 3, and

j is 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3.

More preferred, each M independently from one another represents a bond or is a bridging group, selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_β-, -C(O)-, -CH(OH)-, -(CH₂)_βO-, -(CH₂)_βS-, -(CH₂)_βN(R⁷)-, -O(CH₂)_β, -CHHal-, -CHal₂-, -S-(CH₂)_β- and -N(R⁷)(CH₂)_β, where β is 1 to 6 and especially preferred 1 to 3, Hal is halogen and R⁷ is as defined above. More preferred, the group B of Formula I is a substituted or unsubstituted six member aryl moiety or six member hetaryl moiety, said hetaryl moiety having 1 to 4 members selected from the group of hetaryl atoms consisting

of nitrogen, oxygen and sulfur with the balance of the hetaryl moiety being carbon.

Even more preferred, the group B of Formula I is

- 5 a) an unsubstituted phenyl group, an unsubstituted pyridyl group, an unsubstituted pyrimidinyl, a phenyl group substituted by a substituent selected from the group consisting of halogen and W_γ wherein W and γ are as defined in claim 1, a pyrimidinyl group substituted by a substituent selected from the group constituting of halogen and W_γ ,
10 whereas W and γ are as defined above, or a substituted pyridyl group, substituted by a substituent selected from the group consisting of halogen and W_γ wherein W and γ are as defined above; or a substituted phenyl group, a substituted pyrimidinyl group, or
15 substituted pyridyl group substituted 1 to 3 times by 1 or more substituents selected from the group consisting of $-\text{CN}$, halogen, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkyl alkoxy, $-\text{OH}$, up to per halo substituted $\text{C}_1\text{-C}_{10}$ alkyl, up to per halo substituted $\text{C}_1\text{-C}_{10}$ alkoxy or phenyl substituted by halogen up to per halo; or
20
- b) a substituted phenyl group, a substituted pyrimidinyl group, or substituted pyridyl group substituted 1 to 3 times b 1 or more substituents selected from the group consisting of $-\text{CN}$, halogen, alkyl, especially $\text{C}_1\text{-C}_4$ alkyl, alkoxy, especially $\text{C}_1\text{-C}_4$ alkoxy, $-\text{OH}$, up
25 to per halo substituted alkyl, especially up to per halo substituted $\text{C}_1\text{-C}_4$ alkyl, up to per halo substituted alkoxy, especially up to per halo substituted $\text{C}_1\text{-C}_4$ alkoxy or phenyl substituted by halogen up to per halo.
- 30 In the formula I, the group L which is directly bound to D is preferably a substituted or unsubstituted 6 member aryl moiety or a substituted or unsubstituted 6 member hetaryl moiety, wherein said hetaryl moiety has 1 to 4 members selected from the group of heteroatoms consisting of
35 nitrogen, oxygen and sulfur with the balance of said hetaryl moiety being

carbon, wherein the one or more substituents are selected from the group consisting of halogen and $W\gamma$ wherein W and γ are as defined above.

5 More preferred, the group L is a substituted phenyl, unsubstituted phenyl, substituted pyrimidinyl, unsubstituted pyrimidinyl, substituted pyridyl or unsubstituted pyridyl group.

10 In the formula I, the group L' preferably comprises a 5 to 6 membered aryl moiety or hetaryl moiety, wherein said heteraryl moiety comprises 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulfur.

More preferred, the group L' is phenyl, pyridinyl or pyrimidinyl.

15 According to the invention, a bivalent glycinamide moiety is preferably a bivalent radical derived from substituted or unsubstituted, preferably unsubstituted amide of the amino acid glycine. If the amide of the amino acid glycine is substituted, it is preferably mono substituted on the nitrogen atom of the amide group and/or mono substituted on the nitrogen atom of the amino group. Preferably, the substituted or unsubstituted amide of the
20 amino acid glycine is bonded to A and B via its nitrogen atoms of the amide group and the amino group, respectively. This kind of linkage is usually referred to as an N,N'-linkage. Therefore, D is more preferred an unsubstituted amide of the amino acid glycine, which is bonded to the radicals A and B via its N,N'-atoms. In this respect, one or both of the
25 nitrogen atoms of D can, independently from one another, optionally be deprotonated, protonated and/or quarternized. The resulting ions or salts are also subject of the present invention.

30 As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment,
35 healing, prevention, or amelioration of a disease, disorder, or side effect,

or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

5 As used herein, the term "alkyl" preferably refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C₁-C₆ perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

15 As used herein, the term "C₁-C₆ alkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms. Examples of branched or straight chained "C₁-C₆ alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, t-butyl, n-pentyl and isopentyl.

20 As used herein, the term "alkylene" preferably refers to a straight or branched chain 30 divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

35 As used herein, the term "C₁-C₆ alkylene" preferably refers to an alkylene group, as defined above, which contains at least 1, and at most 6, carbon atoms respectively. Examples of "C₁-C₆ alkylene" groups useful in the

present invention include, but are not limited to, methylene, ethylene and n-Propylene.

As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

5

As used herein, the term "C₁-C₆ haloalkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halogen, halogen being as defined herein.

10

Examples of branched or straight chained "C₁-C₆ haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

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As used herein, the term "C₃-C₇ cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C₁-C₆ alkyl linker through which it may be attached. The C₁-C₆ alkyl group is as defined above. Exemplary "C₃-C₇ cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

20

As used herein, the term "C₃-C₇ cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

30

As used herein, the term "heterocyclic" or the term "heterocyclyl" preferably refers to a three to twelve-membered heterocyclic ring having

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one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O or N, optionally substituted with substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ haloalkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C₁-C₆ perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO₂, O or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Exemplary optional substituents include C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy,

mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C₁-C₆ perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed.

5 Examples of "aryl" groups include, but are not limited to Phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" preferably refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

20 As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a C₁-C₆ alkyl linker, wherein C₁-C₆ alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolylethyl.

As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ haloalkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy,

mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C₁-C₆ perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five - to seven -membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" preferably refers to the group R_aO-, where R_a is alkyl as defined above and the term "C₁-C₆ alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary C₁-C₆ alkoxy groups useful in the present invention include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy.

As used herein, the term "haloalkoxy" preferably refers to the group R_aO- , where R_a is haloalkyl as defined above and the term " C_1-C_6 haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1 and at most 6 carbon atoms.

5 Exemplary C_1-C_6 haloalkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

10 As used herein the term "aralkoxy" preferably refers to the group $R_C R_B O-$, where R_B is alkyl and R_C is aryl as defined above.

As used herein the term "aryloxy" preferably refers to the group $R_C O-$, where R_C is aryl as defined above.

15 As used herein, the term "alkylsulfanyl" preferably refers to the group $R_A S-$, where R_A is alkyl as defined above and the term " C_1-C_6 alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

20 As used herein, the term "haloalkylsulfanyl" preferably refers to the group $R_D S-$, where R_D is haloalkyl as defined above and the term " C_1-C_6 haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 2 and at most 6 carbon atoms.

25 As used herein, the term "alkylsulfenyl" preferably refers to the group $R_A S(O)-$, where R_A is alkyl as defined above and the term " C_1-C_6 alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

30 As used herein, the term "alkylsulfonyl" preferably refers to the group $R_A SO_2-$, where R_A is alkyl as defined above and the term " C_1-C_6 alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

35

As used herein, the term "oxo" preferably refers to the group =O.

As used herein, the term "mercapto" preferably refers to the group -SH.

As used herein, the term "carboxy" preferably refers to the group -COOH.

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As used herein, the term "cyano" preferably refers to the group -CN.

10

As used herein, the term "cyanoalkyl" preferably refers to the group -R_BCN, wherein R_B is alkyl as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

15

As used herein, the term "aminosulfonyl" preferably refers to the group -SO₂NH₂.

20

As used herein, the term "carbamoyl" preferably refers to the group -C(O)NH₂.

As used herein, the term "sulfanyl" shall refer to the group -S-.

As used herein, the term "sulfenyl" shall refer to the group -S(O)-.

25

As used herein, the term "sulfonyl" shall refer to the group -S(O)₂- or -SO₂-.

As used herein, the term "acyl" preferably refers to the group R_FC(O)-, where R_F is alkyl, cycloalkyl or heterocyclyl as defined herein.

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As used herein, the term "aroyl" preferably refers to the group R_CC(O)-, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyl" preferably refers to the group R_EC(O)-, where R_E is heteroaryl as defined herein.

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As used herein, the term "alkoxycarbonyl" preferably refers to the group $R_AOC(O)-$, where R_A is alkyl as defined herein.

As used herein, the term "acyloxy" preferably refers to the group $R_FC(O)O-$, where R_F is alkyl, cycloalkyl, or heterocyclyl as defined herein.

5

As used herein, the term "aroyloxy" preferably refers to the group $R_C C(O)O-$, where R_C is aryl as defined herein.

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As used herein, the term "heteroaroyloxy" preferably refers to the group $R_E C(O)O-$, where R_E is heteroaryl as defined herein.

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As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is common practice in the art.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

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As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

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As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or formula II or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable

solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

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As used herein, the term "substituted" preferably refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

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Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers.

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Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulae I and II above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral Centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formulae (I) or (II) are included within the scope of the compounds of formulae (I) and (II) and preferably the formulae and subformulae corresponding thereto.

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Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as β -camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenyl

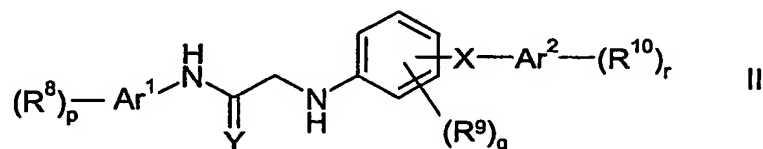
glycine); an example of a suitable eluent is a hexane/isopropanol/ acetonitrile mixture.

The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

It is of course also possible to obtain optically active compounds of the formula I or II by the methods described above by using starting materials which are already optically active.

Unless indicated otherwise, it is to be understood that reference to compounds of formula I preferably includes the reference to the compounds of formula II. Unless indicated otherwise, it is to be understood that reference to the compounds of formula II preferably includes the reference to the sub formulae corresponding thereto, for example the sub formulae II.1 to II.20 and preferably formulae IIa to IIh. It is also understood that the following embodiments, including uses and compositions, although recited with respect to formula I are preferably also applicable to formulae II, sub formulae II.1 to II.20 and preferably formulae IIa to IIh.

Especially preferred compounds according to the invention are compounds of formula II



wherein

Ar^1, Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or

two heteroatoms, independently selected from N, O and S,

- 5 R^8, R^9 and R^{10} are independently selected from a group consisting of
H, A, cycloalkyl 3 to 7 carbon atoms, Hal, CH_2Hal ,
 $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
 $(CH_2)_nNR^8CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$,
 $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$,
10 $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $CH=N-OA$, $CH_2CH=N-OA$,
 $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$, $(CH_2)_nOC(O)NR^{11}R^{12}$,
 $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$,
 $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})$,
 $C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^8$,
15 $(CH_2)_nN(R^8)CH_2CH_2NR^{12}R^8$, $CH=CHCOOR^{13}$,
 $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$,
 $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$,
 $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$,
20 $(CH_2)_nN(CH_2CONH_2)COOR^{13}$,
 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,
 $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$,
 $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein
- 25 R^{11}, R^{12} are independently selected from a group consisting of
H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$,
- R^{13}, R^{14} are independently selected from a group consisting of
H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,
- 30 A is selected from the group consisting of alkyl, alkenyl,
cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,
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- 5 Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- 10 Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- 15 R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^5$, wherein
- 20 Ar^5 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3 ,
- 25 n, m are independently of one another 0, 1, 2, 3, 4, or 5,
- 30 X represents a bond or is $(CR^{11}R^{12})_n$, or $(CHR^{11})_n-Q$ - $(CHR^{12})_i$, wherein
- 35 Q is selected from a group consisting of O, S, $N-R^{17}$, $(CHAl_2)_j$, $(O-CHR^{18})_j$, $(CHR^{18}-O)_j$, $CR^{18}=CR^{19}$, $(O-CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}-O)_j$, C=O, C=S, C= NR^{17} , $CH(OR^{17})$, $C(OR^{17})(OR^{20})$, C(=O)O, OC(=O), OC(=O)O, C(=O) $N(R^{17})$, $N(R^{17})C(=O)$, OC(=O) $N(R^{17})$, $N(R^{17})C(=O)O$, CH=N-O, CH=N- NR^{17} , OC(O) NR^{17} , $NR^{17}C(O)O$, S=O, SO_2 , SO_2NR^{17} and $NR^{17}SO_2$, wherein

- h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6,
and
- j is 1, 2, 3, 4, 5, or 6,
- 5 Y is selected from O, S, NR^{21} , $\text{C(R}^{22}\text{)-NO}_2$, $\text{C(R}^{22}\text{)-CN}$ and C(CN)_2 , wherein
- R^{21} is independently selected from the meanings given for R^{13} , R^{14} and
- 10 R^{22} is independently selected from the meanings given for R^{11} , R^{12} ,
- p, r are independently from one another 0, 1, 2, 3, 4 or 5,
- 15 q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
- u is 0, 1, 2 or 3, preferably 0, 1 or 2,
- 20 and
- Hal is independently selected from a group consisting of F, Cl, Br and I;
- 25 and the salts and solvates thereof, preferably the physiologically acceptable salts and solvates thereof.
- Even more preferred are compounds of formula II
- 30 wherein
- Ar^1 , Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or
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aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

- 5 R^8 , R^9 and R^{10} are independently selected from a group consisting of
H, A, cycloalkyl 3 to 7 carbon atoms, Hal, CH_2Hal ,
 $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
10 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$,
 $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$,
 $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$,
 $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$,
 $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$,
15 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})$,
 $C(R^{13})HCOOR^8$, $(CH_2)_nN(COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$,
 $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CH_2CONH_2)COOR^{13}$,
20 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,
 $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,
- X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h-Q$ -
 $(CHR^{12})_i$, wherein
- 25 Q is selected from a group consisting of O, S, $N-R^{17}$,
 $(CHAl_2)_j$, $(O-CHR^{18})_j$, $(CHR^{18}-O)_j$, $CR^{18}=CR^{19}$, $(O-$
 $CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}-O)_j$, $C=O$, $C=NR^{17}$,
 $CH(OR^{17})$, $C(OR^{17})(OR^{20})$, $C(=O)N(R^{17})$, $N(R^{17})C(=O)$,
30 $CH=N-NR^{17}$, $S=O$, SO_2 , SO_2NR^{17} and $NR^{17}SO_2$,
wherein
- h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6,
preferably 0, 1, 2 or 3 and

j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

r is 0, 1, 2, or 3, preferably 0, 1 or 2;

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and the salts and solvates thereof, preferably the physiologically acceptable salts and solvates thereof.

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Subject of the present invention are especially compounds of formula I and II, in which one or more substituents or groups, preferably the major part of the substituents or groups has a meaning which is indicated as preferred, more preferred, even more preferred or especially preferred.

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In compounds of formula II, the term alkyl preferably refers to an unbranched or branched alkyl residue, preferably an unbranched alkyl residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or 6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a branched alkyl residue comprising 3, 4, 5, 6, 7, 8, 9 or 10, preferably 3, 4, 5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be optionally substituted, especially by one or more halogen atoms, for example up to perhaloalkyl, by one or more hydroxy groups or by one or more amino groups, all of which can optionally be substituted by alkyl. If an alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5 halogen atoms, depending on the number of carbon atoms of the alkyl residue. For example, a methyl group can comprise, 1, 2 or 3 halogen atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by hydroxy groups, it usually comprises one or two, preferably one hydroxy groups. If the hydroxy group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred

unsubstituted. According to compounds of formula II, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further
5 preferred of the group consisting of 2-butyl, n-pentyl, neo-nentyl, isopentyl, hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isopropyl and tert.-butyl.

10 In compounds of formula II, alkenyl is preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

15 In compounds of formula II, alkylene is preferably unbranched and is more preferably methylene or ethylene, furthermore preferably propylene or butylene.

20 In compounds of formula II, alkylencycloalkyl preferably has 5 – 10 carbon atoms and is preferably methylenecyclopropyl, methylenecyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or ethylenecycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.

25 In compounds of formula II, the term "alkoxy" preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group is defined above. More preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives
30 are selected from the group consisting of O-CCl₃, O-CF₃, O-C₂Cl₅, O-C₂F₅, O-C(CCl₃)₃ and O-C(CF₃)₃.

35 In compounds of formula II, the term "alkoxyalkyl" preferably comprises branched and unbranched residues, more preferred unbranched residues,

of formula $C_uH_{2u+1}-O-(CH_2)_v$, wherein u and v are independently from each other 1 to 6. Especially preferred is $u = 1$ and v 1 to 4.

5 In compounds of formula II the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

10 In compounds of formula II, cycloalkyl preferably has 3 – 7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl.

15 In compounds of formula II, Ar^3 to Ar^6 are preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally substituted by one or more substituents, selected from the group consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$.

20 In compounds of formula II, het is preferably an optionally substituted aromatic heterocyclic residue and even more preferred and optionally substituted saturated heterocyclic residue, wherein the substituents are preferably selected from A, CN and hal. Even more preferred, het is selected from the group consisting of 1-piperidyl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 4-morpholinyl, 1-4pyrrolidinyl, 25 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, chinolinyl, isochinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl. Especially the thiophenyl and the 30 pyridyl residues can optionally be substituted by one or more cyano groups.

Preferably, the sum of h and l exceeds 0.

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A preferred aspect of the instant invention relates to compounds of formula II, wherein n is 0 or 1 and especially 0.

5 Another preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 in the residues R^8 , R^9 and/or R^{10} and especially in R^{10} .

10 Another preferred aspect of the instant invention relates to compounds of formula II, wherein X represents a bridging group, selected from $(CR^{11}R^{12})_h$ or $(CHR^{11})_h-Q-(CHR^{12})_i$.

The invention relates in particular to compounds of the formula II in which at least one of said radicals has one of the preferred meanings given above.

15 Some mere preferred groups of compounds may be expressed by the following sub-formulae II.1) to II.20), which correspond to the formula II and in which radicals not denoted in greater detail are as defined in the formula II, but in which

20 II.1) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl;

25 II.2) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl, and

p is 1, 3 or 3;

30 II.3) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,

35 p is 1, 2 or 3, and

- 5 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$;
- 10 II.4) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- p is 1, 2 or 3,
- 15 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$;
- 20 II.5) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 25 p is 1, 2 or 3,
- R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein
- 30 n is 0 or 1;

- II.6) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 5 p is 1, 2 or 3,
- R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, 10 $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein
- n is 0 or 1, and
- 15 u is 0;
- II.7) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 20 p is 1, 2 or 3,
- R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, 25 $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein
- 30 n is 0 or 1,
- u is 0, and
- 35 q is 0 or 1, and

- X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S;
- 5 II.8) Ar¹ is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 10 p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², 15 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein
- n is 0 or 1,
- 20 u is 0, and
- q is 0 or 1, and
- 25 X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- 30 Ar² is phenyl or pyridinyl;
- II.9) Ar¹ is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,

- p is 1, 2 or 3,
- 5 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein
- 10 n is 0 or 1,
- u is 0, and
- q is 0 or 1, and
- 15 X is selected from the group consisting of O, S, NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , CH_2CH_2O , preferably O, S and CH_2 and especially O and S,
- 20 Ar^2 is phenyl or pyridinyl, and
- 25 R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,
- 30
- 35 II.10) Ar^1 is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,

- 5 p is 1, 2 or 3,
 R⁸ is selected from the group consisting of alkyl comprising
 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon
 atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising
 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein
 10 n is 0 or 1,
 u is 0, and
 q is 0 or 1, and
 15 X is selected from the group consisting of O, S, NR¹¹,
 CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂,
 CH₂CH₂O, preferably O, S and CH₂ and especially O
 and S,
 20 Ar² is phenyl or pyridinyl, and
 R¹⁰ is selected from the group consisting of alkyl comprising
 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon
 atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising
 25 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl
 comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and
 30 especially (CH₂)_nCONR¹¹R¹², wherein
 n is 0, 1 or 2, preferably 0 or 1;

- II.11) Ar¹ is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 5 p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 10 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein
- n is 0 or 1,
- 15 u is 0, and
- q is 0 or 1, and
- 20 X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- 25 Ar² is phenyl or pyridinyl, and
- R¹⁰ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 30 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- 35

- n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- 5 II.12) p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², 10 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein
- n is 0 or 1,
- 15 u is 0, and
- q is 0 or 1, and
- 20 X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- 25 Ar² is phenyl or pyridinyl, and
- R¹⁰ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², 30 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- 35

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

5 II.13) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

10 n is 0 or 1,

u is 0, and

15 q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , CH_2CH_2O , preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl or pyridinyl, and

25 R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

35 n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

II.14) R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,

Ar² is phenyl or pyridinyl, and

R¹⁰ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

- Ar² is phenyl or pyridinyl, and
- R¹⁰ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- II.17) X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- Ar² is phenyl or pyridinyl, and
- R¹⁰ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

II.18) Ar^2 is phenyl or pyridinyl, and

5 R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl
10 comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,

15 n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

20 II.19) R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl
25 comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,

n is 0, 1 or 2, preferably 0 or 1 and

30 r is 0, 1 or 2, preferably 0 or 1;

35 II.20) R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,

$(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, preferably alkyl
 comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and
 especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, and

5

r is 0, 1 or 2, preferably 0 or 1.

10

One preferred embodiment of the instant invention relates to compounds
 of formula II and preferably one or more of sub formulae II.1) to II.20),
 wherein p is 1, 2 or 3 and R^8 is independently selected from the group
 consisting of methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br, CF_3 , $\text{C}(\text{CF}_3)_3$,
 methoxy, ethoxy, tert.-butoxy, perfluoro tert.-butoxy ($\text{OC}(\text{CF}_3)_3$), methyl
 sulfanyl (SCH_3), ethyl sulfanyl (SCH_2CH_3), acetyl (COCH_3), propionyl
 (COCH_2CH_3), butyryl ($\text{COCH}_2\text{CH}_2\text{CH}_3$). If p is 2 or 3, all substituents can
 be the same or different.

15

20

Another preferred embodiment of the instant invention relates to
 compounds of formula II and preferably one or more of sub formulae II.1)
 to II.20), wherein X is selected from the group consisting of S, N-R^{21} , CH_2 ,
 CH_2CH_2 , OCH_2 and CH_2O .

25

Another preferred embodiment of the instant invention relates to
 compounds of formula II and preferably one or more of sub formulae II.1)
 to II.20), wherein X is selected from the group consisting of S, CH_2 .

30

Another even more preferred embodiment of the instant invention relates
 to compounds of formula II and preferably one or more of sub formulae
 II.1) to II.20), wherein X is O.

35

Another preferred embodiment of the instant invention relates to
 compounds of formula II and preferably one or more of sub formulae II.1)
 to II.20), wherein Y is selected from the group consisting of $\text{C}(\text{R}^{22})\text{-NO}_2$,
 $\text{C}(\text{R}^{22})\text{-CN}$ and $\text{C}(\text{CN})_2$.

Another more preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is selected from the group consisting of O, S and NR^{21} .

5 Another even more preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is selected from the group consisting of O and S.

10 Another even more preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is O.

15 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Ar^2 is pyridinyl.

20 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein r is either 0 or 1. If r is 1, R^{10} is preferably $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, wherein n is 0. In this embodiment, R^{11} is preferably selected from the group consisting of H and A and more preferred from H and alkyl, and R^{12} is preferably selected from the group consisting of H and A and more preferred from H and alkyl. Especially preferred as residue R^{10} are carbamoyl, more preferred alkyl carbamoyl or diaalkyl carbamoyl, even more preferred methyl carbamoyl or dimethyl carbamoyl, ethyl carbamoyl or diethyl carbamoyl and especially preferred methyl carbamoyl ($-\text{CONHCH}_3$). This embodiment is especially preferred when Ar^2 is pyridinyl. When Ar^2 is pyridinyl, R^{10} is preferably bonded in a vicinal position to the nitrogen atom of the pyridinyl residue, i.e. in 2- and/or 6-position of the pyridinyl residue.

30 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Ar^1 comprises two or more substituents R^8 , wherein one or more, preferably one substituent R^8 is selected from the group consisting of $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_m\text{OR}^{12}$,
35

$(\text{CH}_2)_n\text{O}(\text{CH}_2)_m\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_m\text{NR}^{12}\text{R}^{12}$, $(\text{CH}_2)_n\text{COOR}^{13}$ and $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is preferably 0, 1 or 2, especially 0, m is 1 or 2, and u is preferably 2. In this embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this

5 embodiment, one substituent R^8 is especially preferably selected from the group consisting of NH_2 , $\text{N}(\text{CH}_3)_2$, $\text{N}(\text{C}_2\text{H}_5)_2$, $\text{NHCH}_2\text{CH}_2\text{NH}_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{NH}_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, SCH_3 , SC_2H_5 , SO_2CH_3 , COOCH_3 and COOH .

10 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein q is 0, i.e. the phenyl group bound to the amino group of the glycine amide moiety is unsubstituted.

15 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of formulae II.1) to II.20), wherein $(\text{R}^8)_p\text{-Ar}^1$ is selected from the group consisting of 3-acetyl-phenyl, 4-acetyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-bromo-2-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-bromo-3-

20 trifluoromethyl-phenyl, 2-chloro-phenyl, 2-chloro-4-trifluoromethyl-phenyl, 2-chloro-5-trifluoromethyl-phenyl, 3-chloro-phenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-chloro-phenyl, 4-chloro-2-trifluoromethyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl,

25 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 5-chloro-2-methoxy-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichloro-phenyl, 3,4-dichloro-phenyl, 3,5-dichloro-phenyl, 2,4,5-trichloro-phenyl, 4-fluoro-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-ethoxy-phenyl, 2-methoxy-phenyl, 2-methoxy-5-trifluoromethyl-phenyl, 4-methoxy-phenyl,

30 2,5-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 3-methoxy-phenyl, 3-methylsulfanyl-phenyl, 4-methylsulfanyl-phenyl, o-tolyl (2-methyl-phenyl), m-tolyl (3-methyl-phenyl), p-tolyl (4-methyl-phenyl), 2,3-dimethyl-phenyl, 2,3-di-

35 methyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-

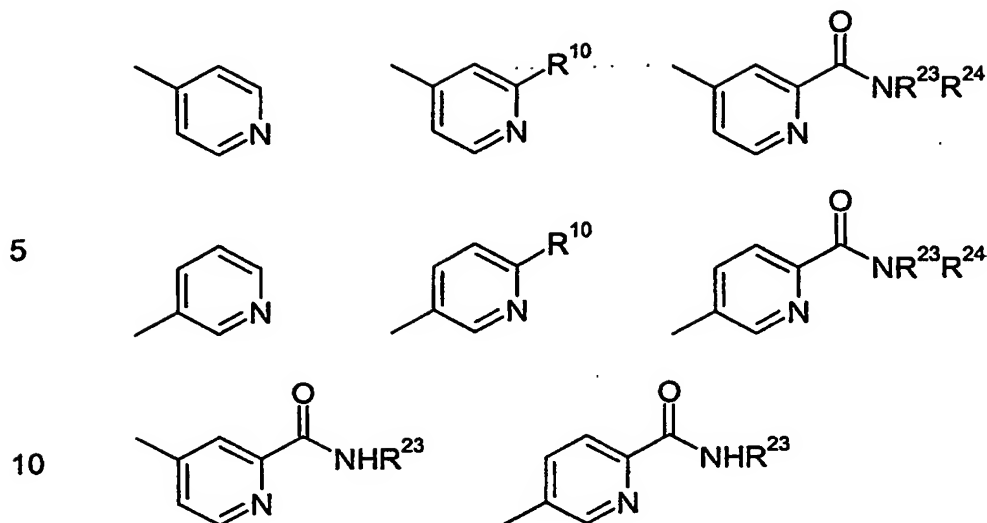
phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 4-isopropyl-phenyl, 4-tert-butyl-phenyl and 5-tert-butyl-isoxazol-3-yl.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein $(R^8)_p-Ar^1$ is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^8 and more preferably selected from the group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_mOR^{12}$, $(CH_2)_nO(CH_2)_mNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_mNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is preferably 0, 1 or 2, especially 0, m is 1 or 2, and u is preferably 2. In this embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SC_2H_5 , SO_2CH_3 , $COOCH_3$ and $COOH$.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.29), wherein X is bonded in the para- (p -) or metha- (m -)position to the phenyl residue that is bonded directly to amino group of the glycine amide moiety.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Ar^2 is a pyridinyl residue and wherein said pyridinyl residue is bonded to X in the 3- or 4-position, preferably the 4-position, relative to the nitrogen atom of the pyridinyl residue.

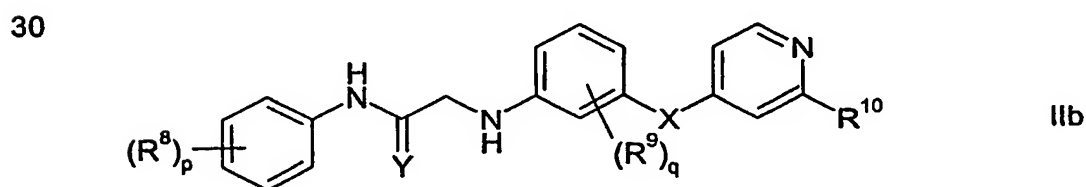
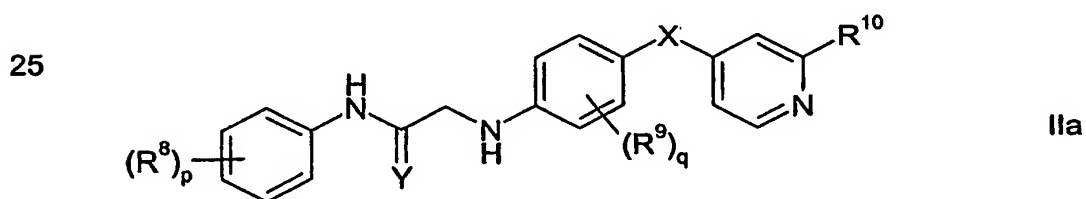
Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein $-Ar^2-(R^{10})$ is selected from the formulae



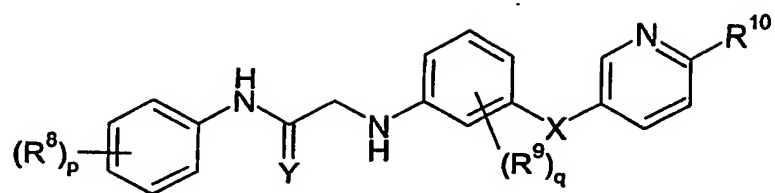
wherein R¹⁰, R²³ and R²⁴ are as defined above and below.

15 Another especially preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein one or more features of the above and below mentioned embodiments are combined in one compound.

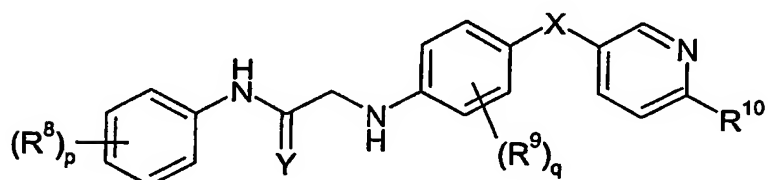
20 Subject of the present invention are therefore especially preferred compounds of formula II according to one or more of the formulae IIa, IIb, IIc, IIe, IIg and IIh,



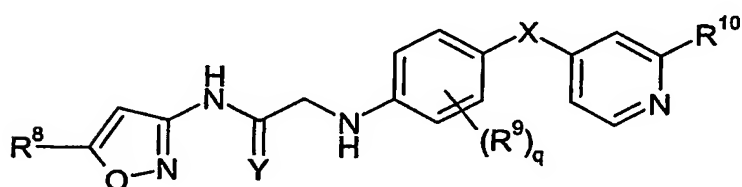
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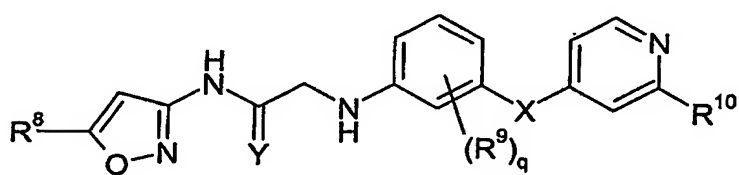
IIc



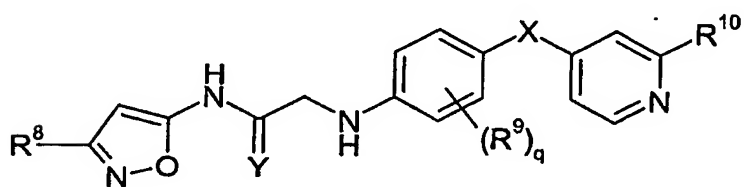
IIId



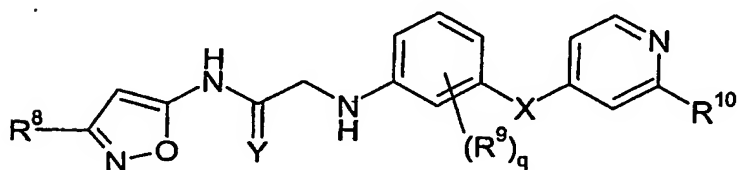
IIe



IIIf



IIg



IIh

wherein R^8 , p, Y, R^9 , q and R^{10} are as defined above and below, and preferably as defined in sub formulae II.1) to II.20) and/or the embodiments related thereto.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20) and IIa to IIh, wherein R^{10} is a substituted carbamoyl moiety

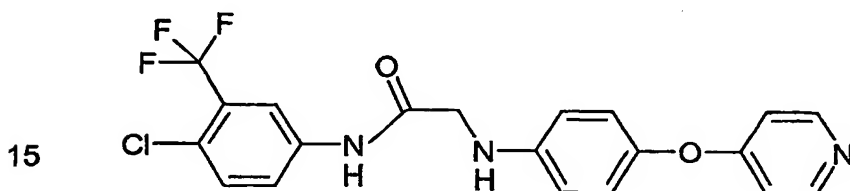
CONHR^{23} or $\text{CONR}^{23}\text{R}^{24}$, preferably CONHR^{23} , wherein R^{23} and R^{24} are independently selected from the definitions given for R^8 , more preferably selected from $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{OR}^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of $\text{CH}_2\text{CH}_2\text{NH}_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{OCH}_3$ and $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$.

It is understood that when a residue, for example R^8 , R^9 , R^{10} or R^{14} or R^{23} , is comprised twice or more times in one or more of the formulae I, II and the sub formulae corresponding thereto, it is in each case independently from one another selected from the meanings given for the respective residue. For example, R^{11} and R^{12} are defined to be independently selected from a group consisting of H, A, $(\text{CH}_2)_m\text{Ar}^3$ and $(\text{CH}_2)_m\text{Het}$. Then $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_m\text{NR}^{12}\text{R}^{12}$ can be $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NA}_2$ (if $R^{11} = \text{A}$, $R^{12} = \text{A}$ and $R^{12} = \text{H}$) as well as $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NHA}$ (if $R^{11} = \text{A}$, $R^{12} = \text{H}$ and $R^{12} = \text{A}$ or $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NH}(\text{CH}_2)_m\text{Het}$ (if $R^{11} = \text{A}$, $R^{12} = \text{H}$ and $R^{12} = (\text{CH}_2)_m\text{Het}$). Accordingly, if a compound of formula II comprises one residue R^8 , R^9 and R^{10} , then for example R^8 , R^9 and R^{10} can all be $(\text{CH}_2)_n\text{COOR}^{13}$, wherein all residues R^{13} are the same (for example CH_2Hal , wherein Hal is Cl; then all residues R^8 , R^9 and R^{10} are the same) or different (for example CH_2Hal , wherein in R^8 Hal is Cl; in R^9 Hal is F; and in R^{10} Hal is Br; then all residues R^8 , R^9 and R^{10} are different); or for example R^8 is $(\text{CH}_2)_n\text{COOR}^{13}$, R^9 is NO_2 and R^{10} is $(\text{CH}_2)_n\text{SR}^{11}$, wherein R^{11} and R^{13} can be the same (for example both can be H or both can be A which is methyl) or different (for example R^{11} can be H and R^{13} can be A which is methyl).

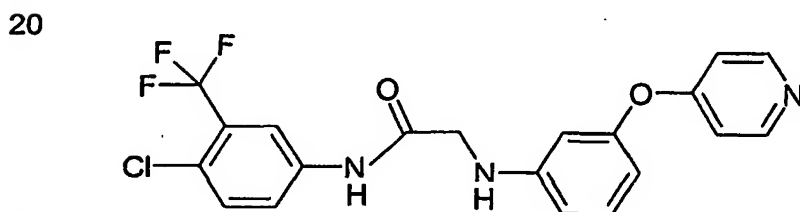
If not stated otherwise, reference to compounds of formula I and formula II also includes the sub formulae related thereto, especially sub formulae II.1) to II.20) and IIa to IIh.

5 Subject of the instant invention are especially those compounds of formula I and/or formula II, in which at least one of the residues mentioned in said formulae has one of the preferred or especially preferred meanings given above and below.

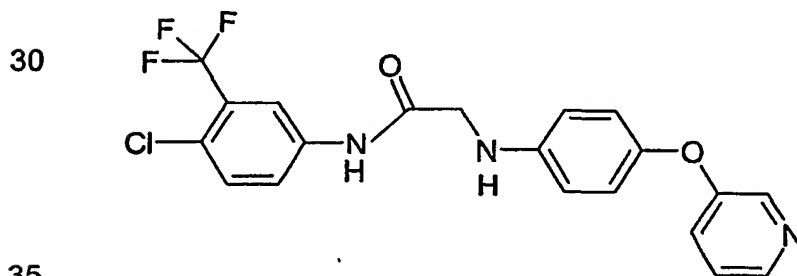
10 The present invention further relates to compounds (1) to (8) as given below:



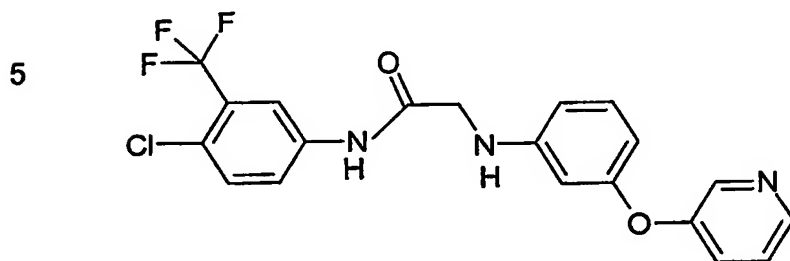
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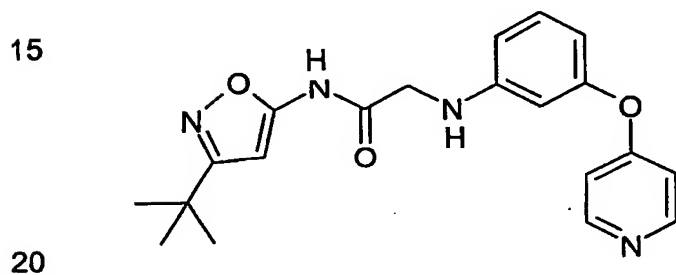
(2): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[3-(pyridin-4-yloxy)-phenylamino]-acetamide (EMD 406024)



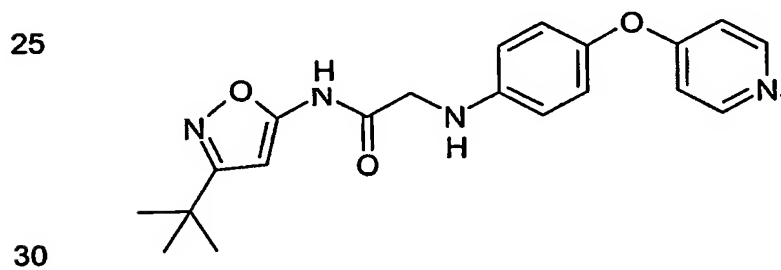
(3): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[4-(pyridin-3-yloxy)-phenylamino]-acetamide (EMD 408673)



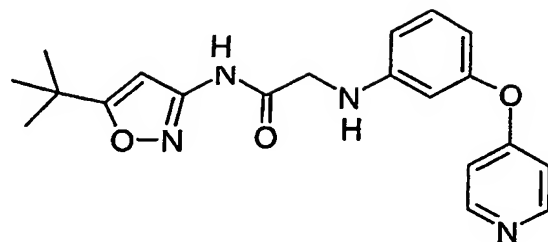
(4): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[3-(pyridin-3-yloxy)-phenylamino]-acetamide (EMD 408674)



(5): N-(3-tert.-Butyl-isoxazol-5-yl)-2-[3-(pyridin-4-yloxy)-phenylamino]-acetamide (EMD 406078)

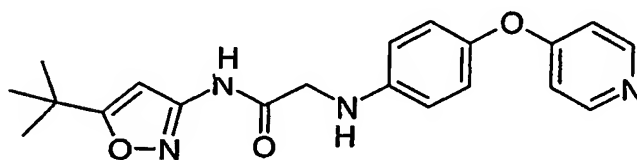


(6): N-(3-tert.-Butyl-isoxazol-5-yl)-2-[4-(pyridin-4-yloxy)-phenylamino]-acetamide (EMD 408672)



5

(7): N-(5-tert-Butyl-isoxazol-3-yl)-2-[3-(pyridin-4-yloxy)-phenylamino]-acetamide (EMD 406081)



10

(8): N-(5-tert-Butyl-isoxazol-3-yl)-2-[4-(pyridin-4-yloxy)-phenylamino]-acetamide (EMD 406082)

15

The present invention also relates to compounds (9) to (232) of formula A-NH-CO-CH₂-NH-B, wherein A and B are as given in the table below:

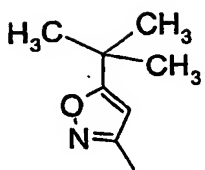
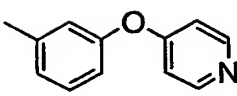
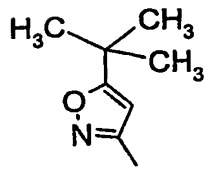
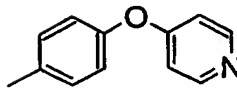
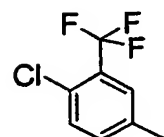
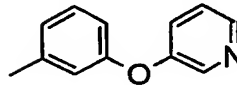

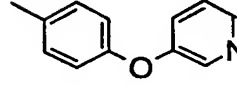
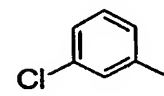
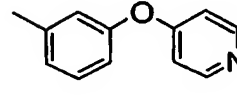
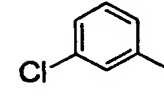
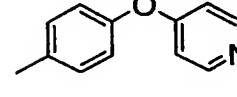
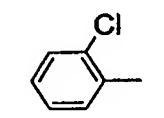
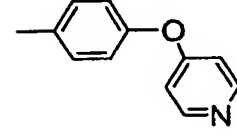
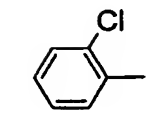
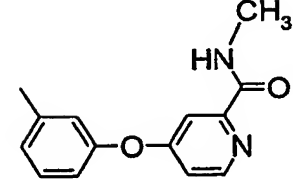
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	A	B
(9)		
(10)		

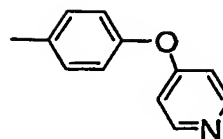
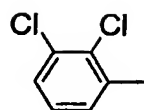
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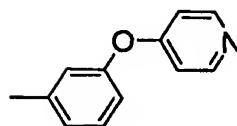
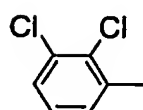
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5	(12)		
10	(13)		
15	(14)		
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30	(17)		
35	(18)		

(19)



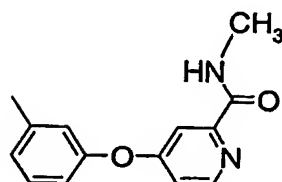
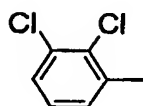
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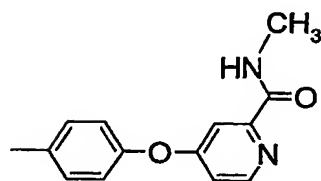
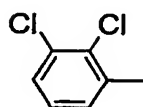
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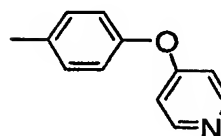
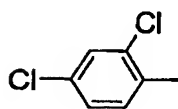
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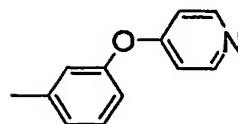
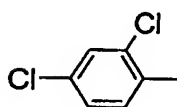
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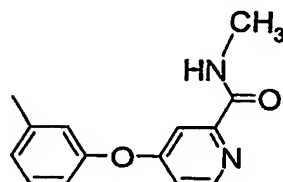
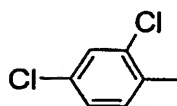
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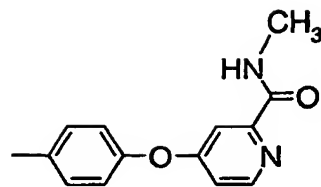
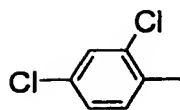
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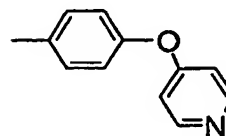
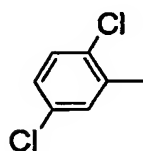
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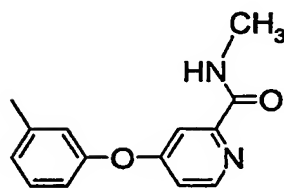
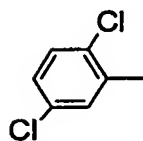
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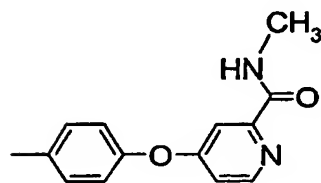
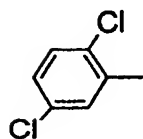
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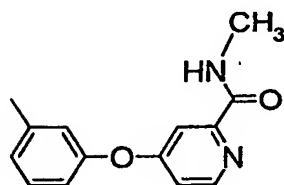
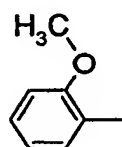
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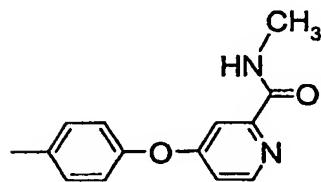
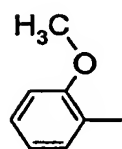
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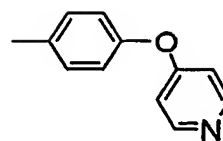
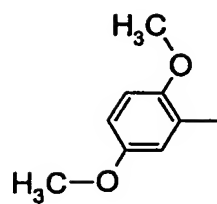
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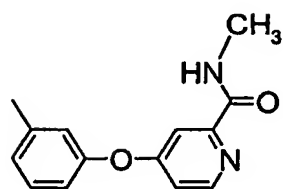
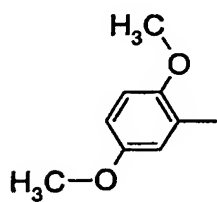
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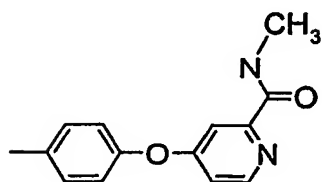
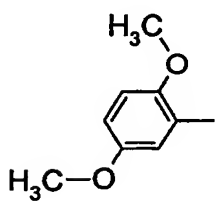
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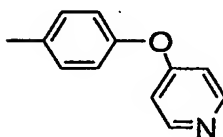
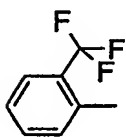
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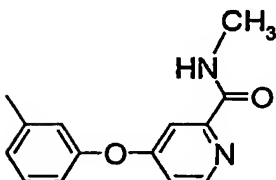
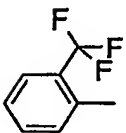
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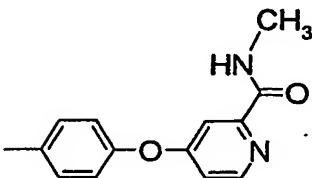
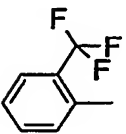
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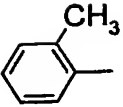
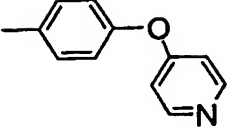
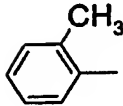
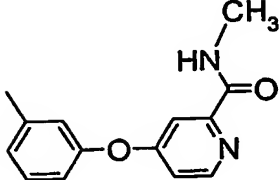
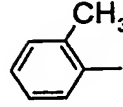
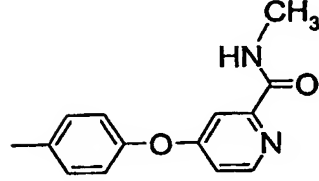
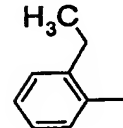
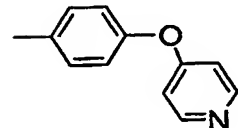
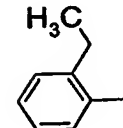
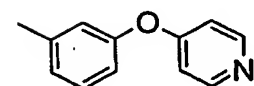
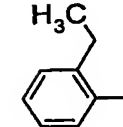
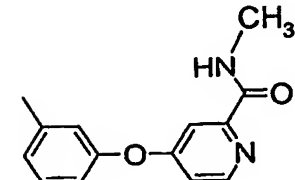
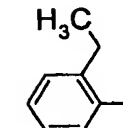
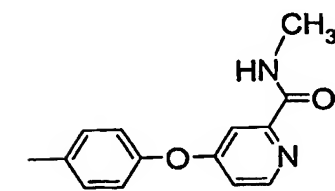
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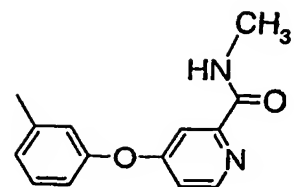
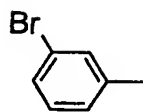


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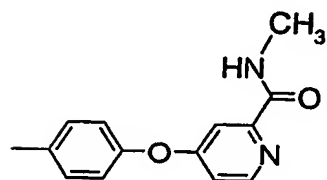
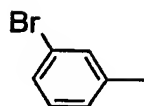
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30	(44)		
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(45)



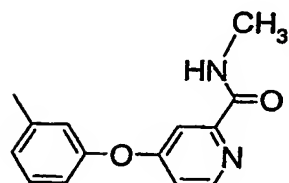
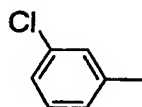
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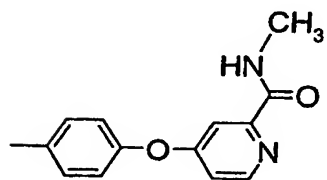
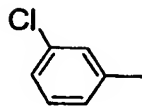
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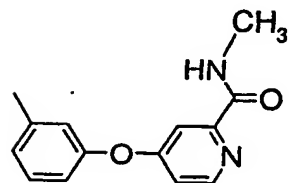
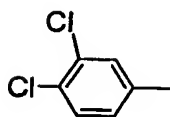
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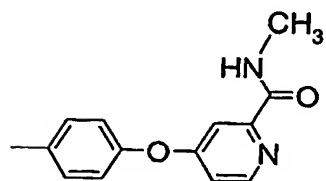
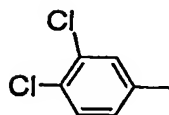
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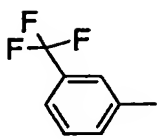
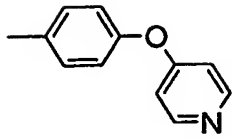
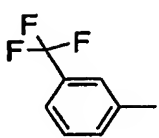
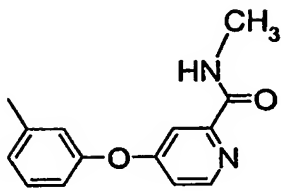
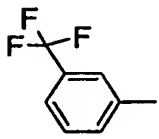
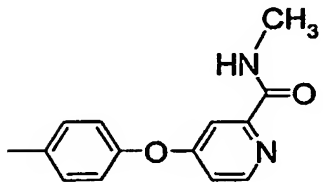
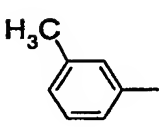
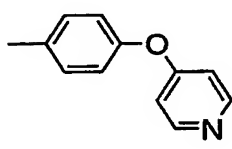
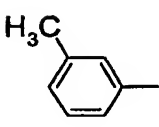
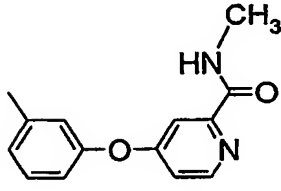
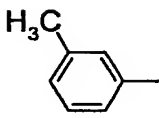
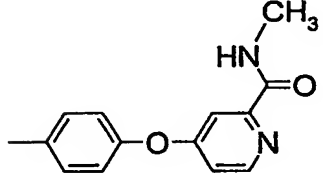
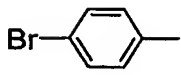
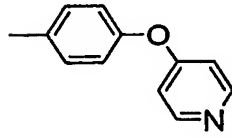
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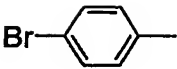
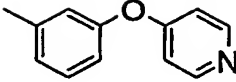
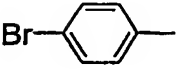
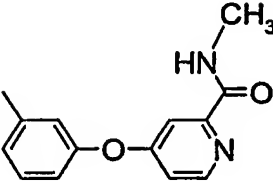
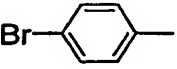
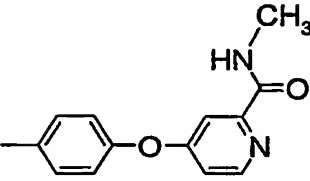

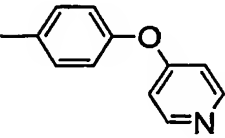
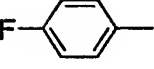
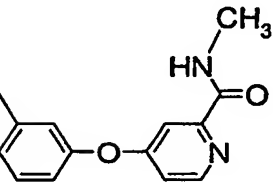
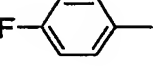
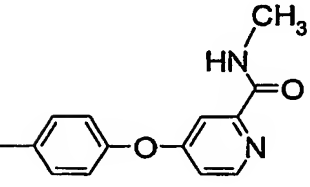
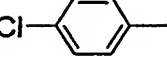
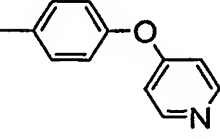
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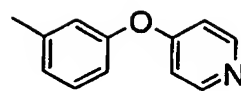
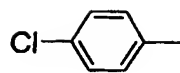
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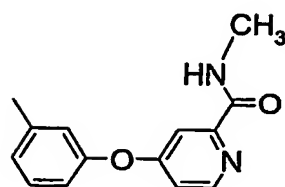
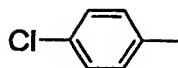
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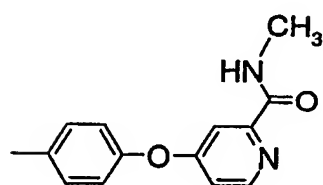
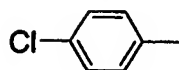
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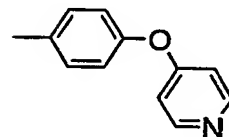
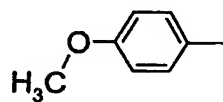
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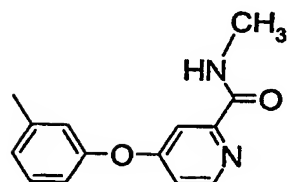
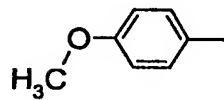
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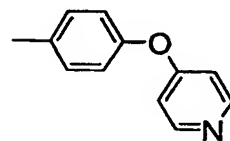
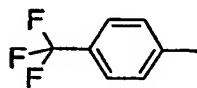
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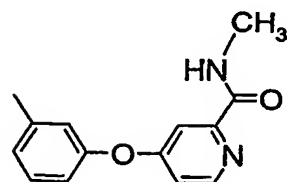
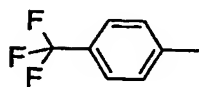
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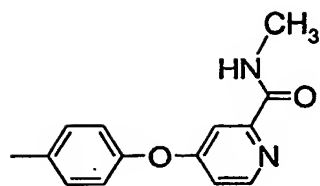
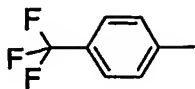
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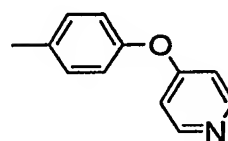
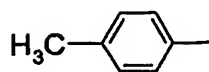
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(72)



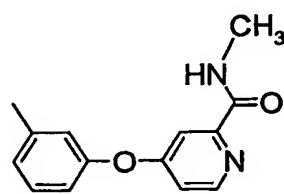
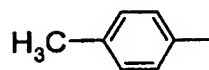
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(73)



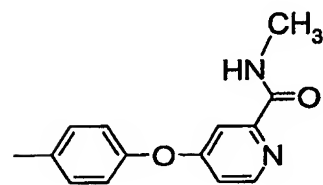
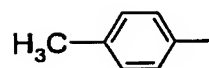
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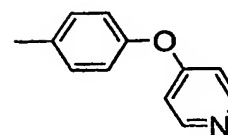
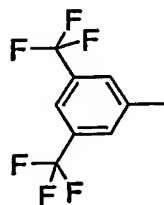
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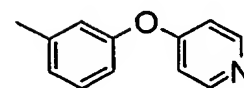
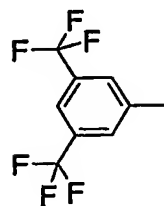
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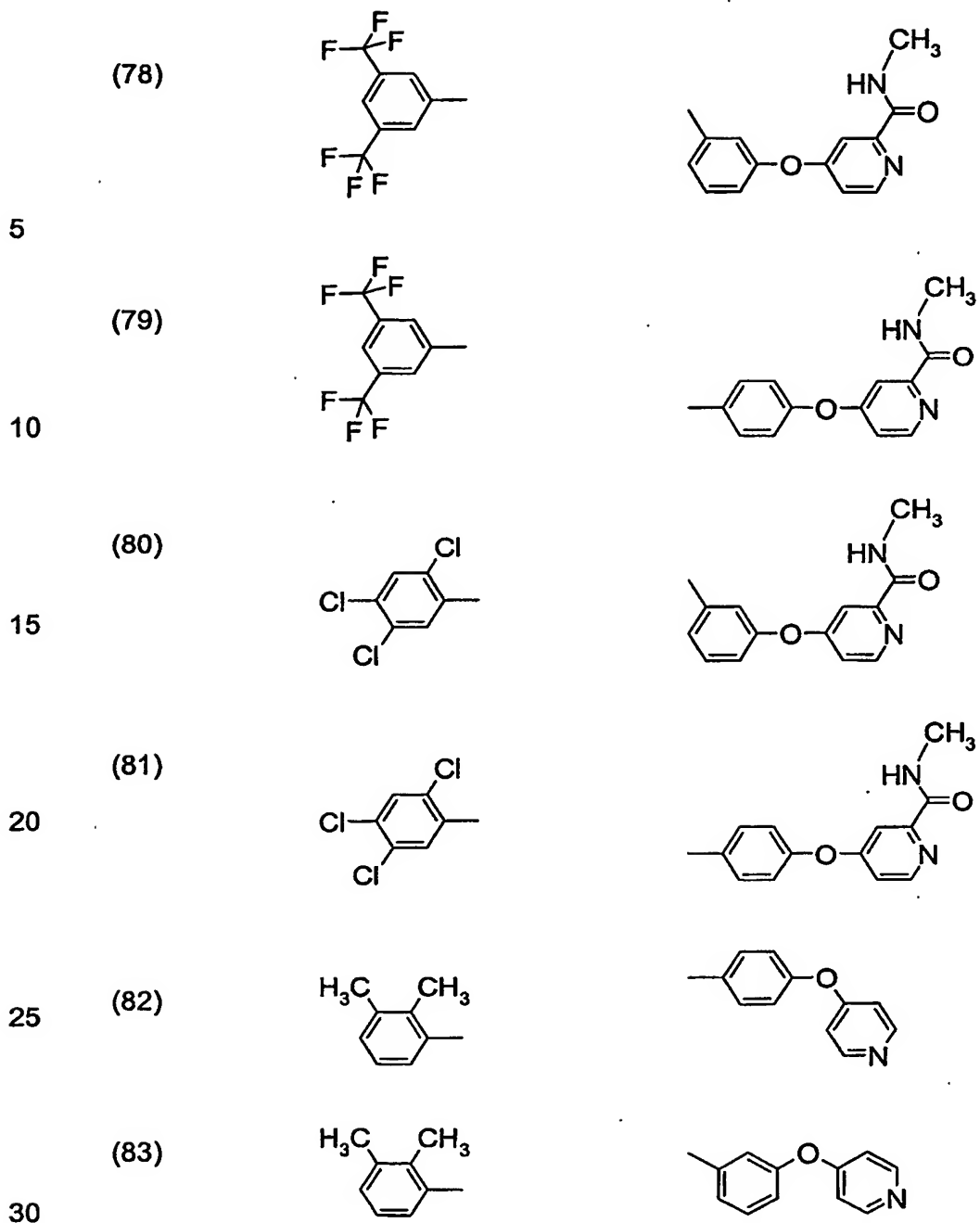
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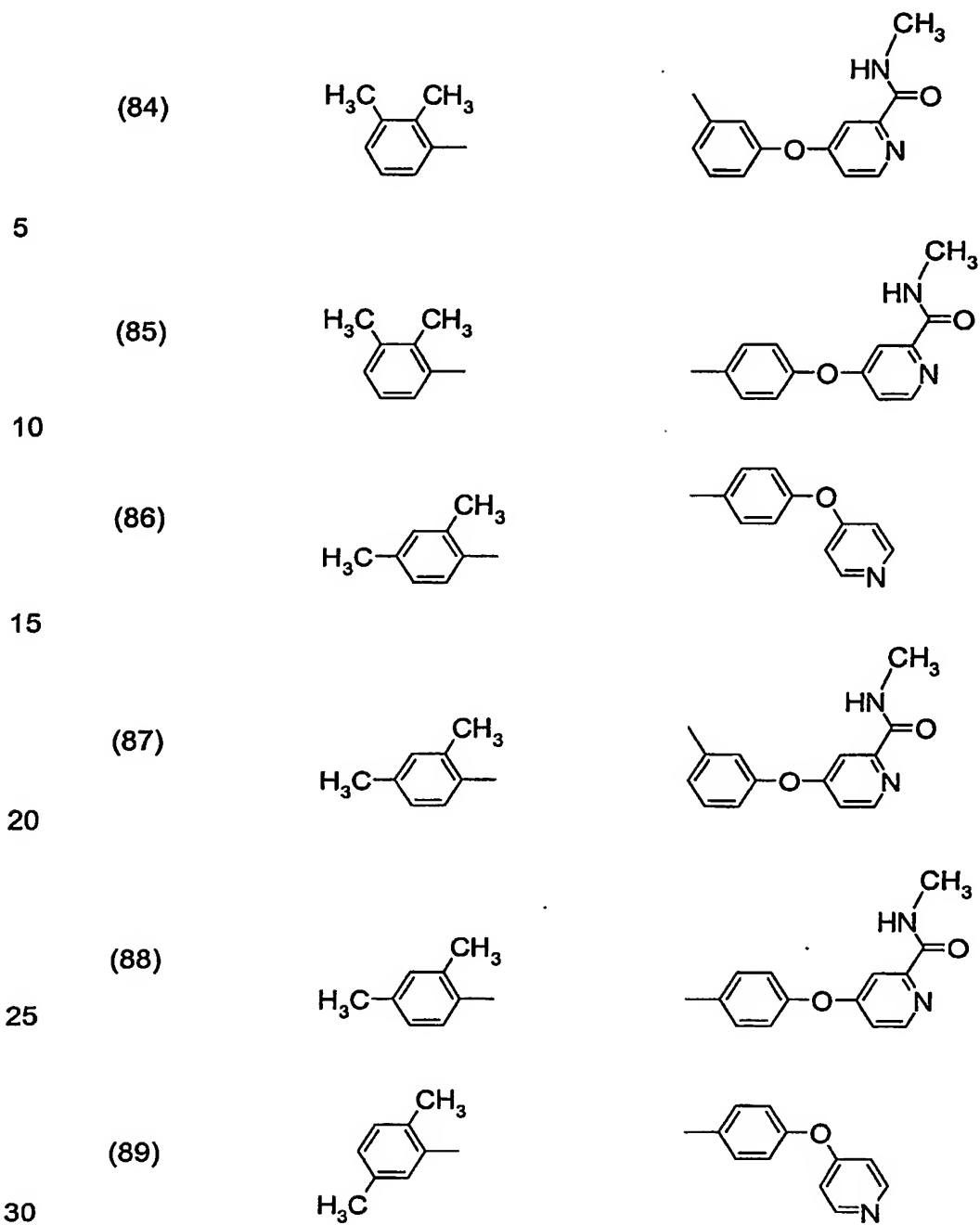
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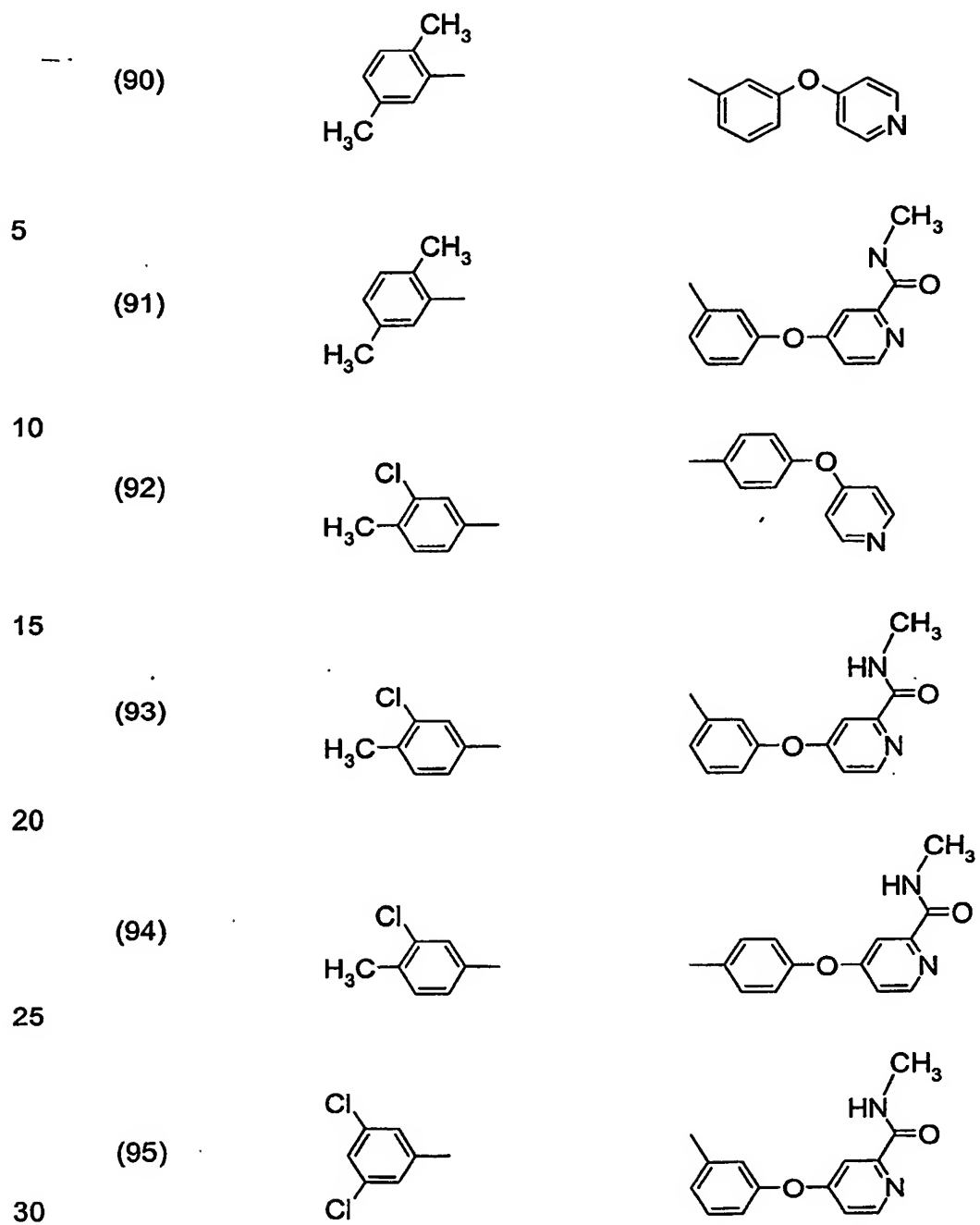


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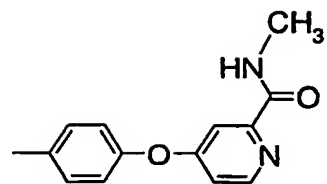
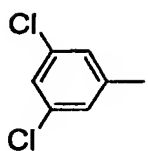
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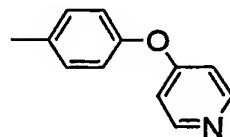
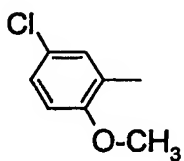


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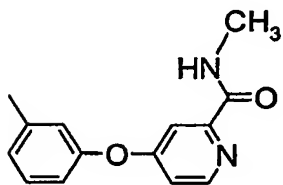
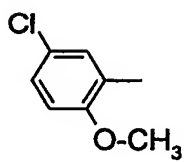
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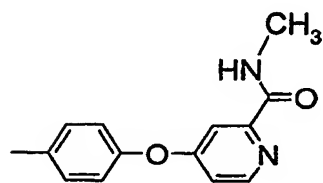
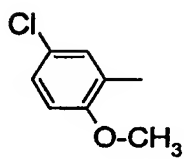
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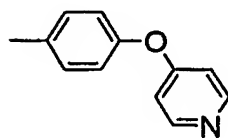
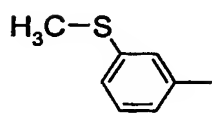
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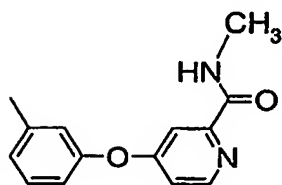
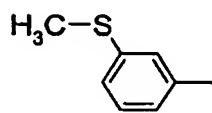
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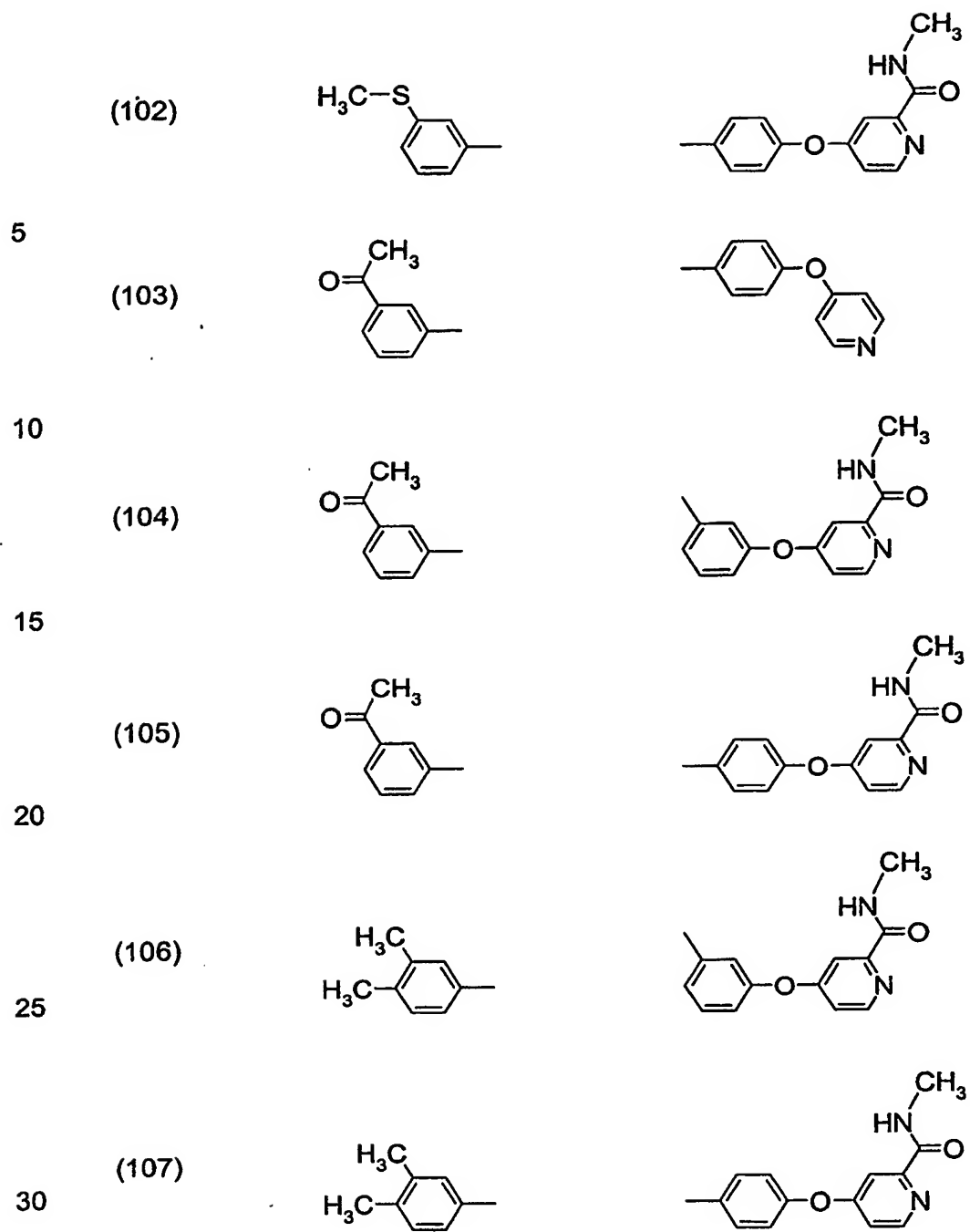
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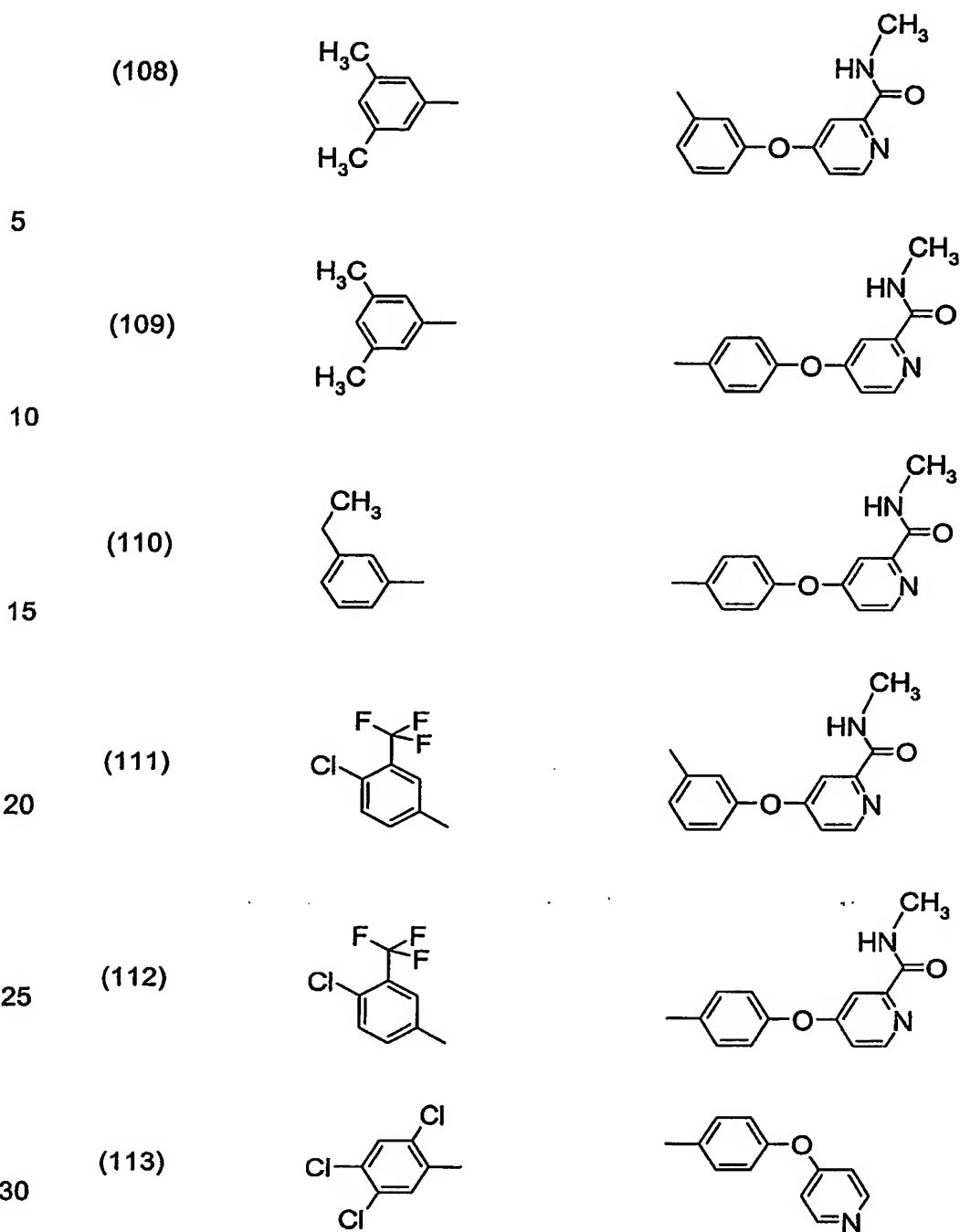
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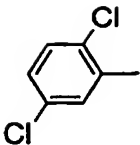
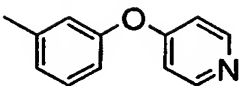
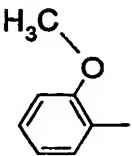
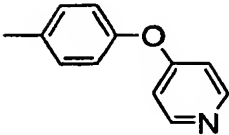
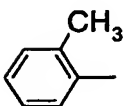
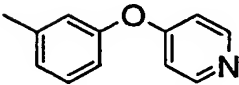
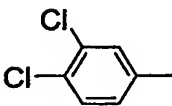
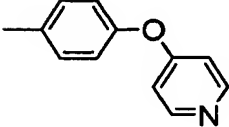
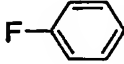
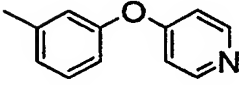
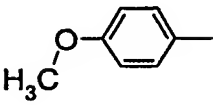
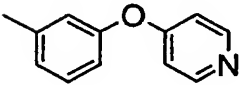
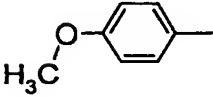
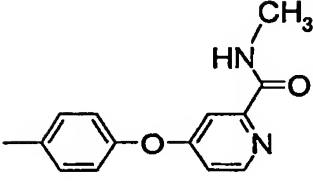
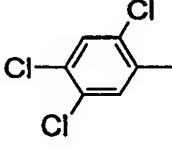
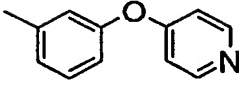


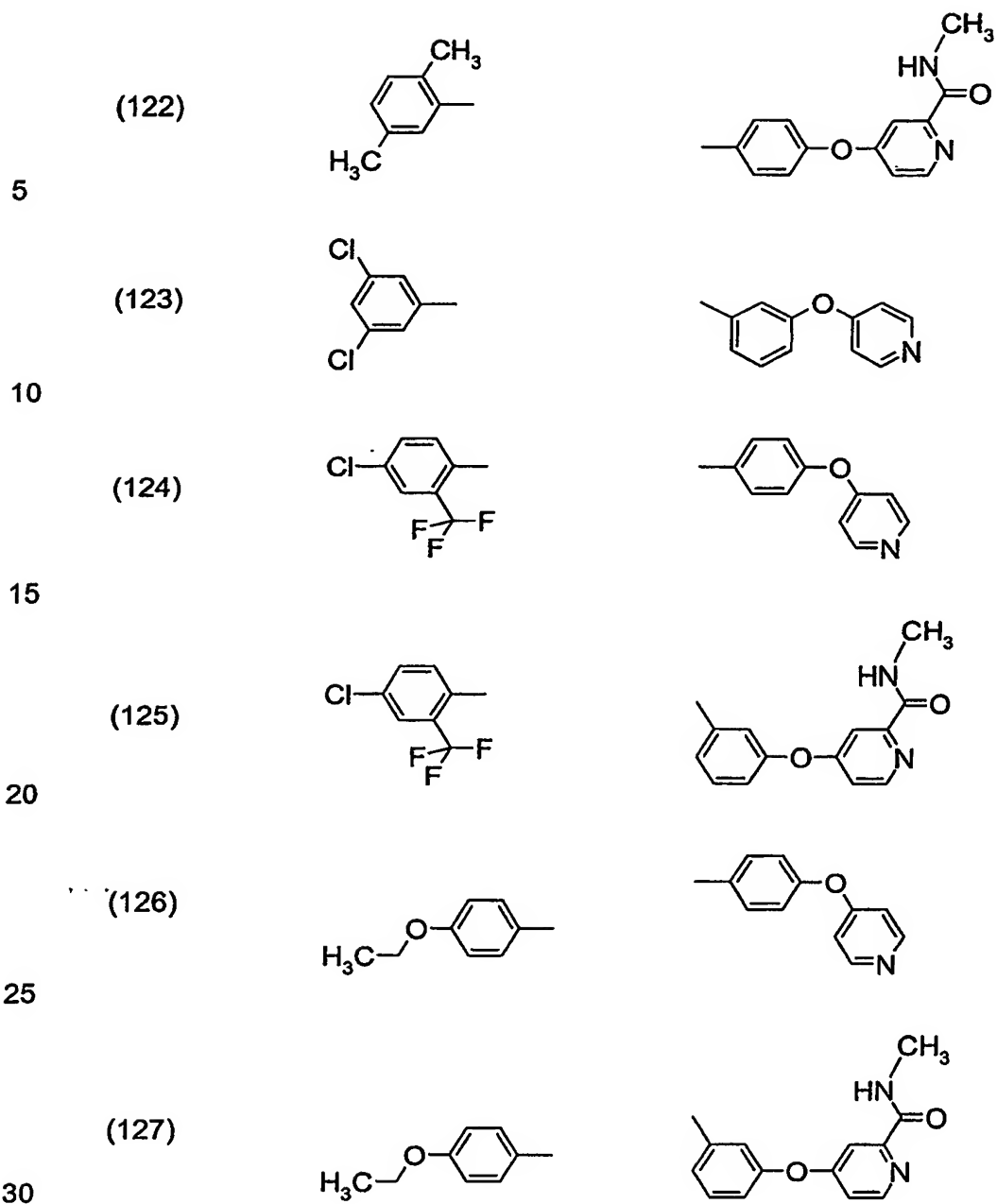
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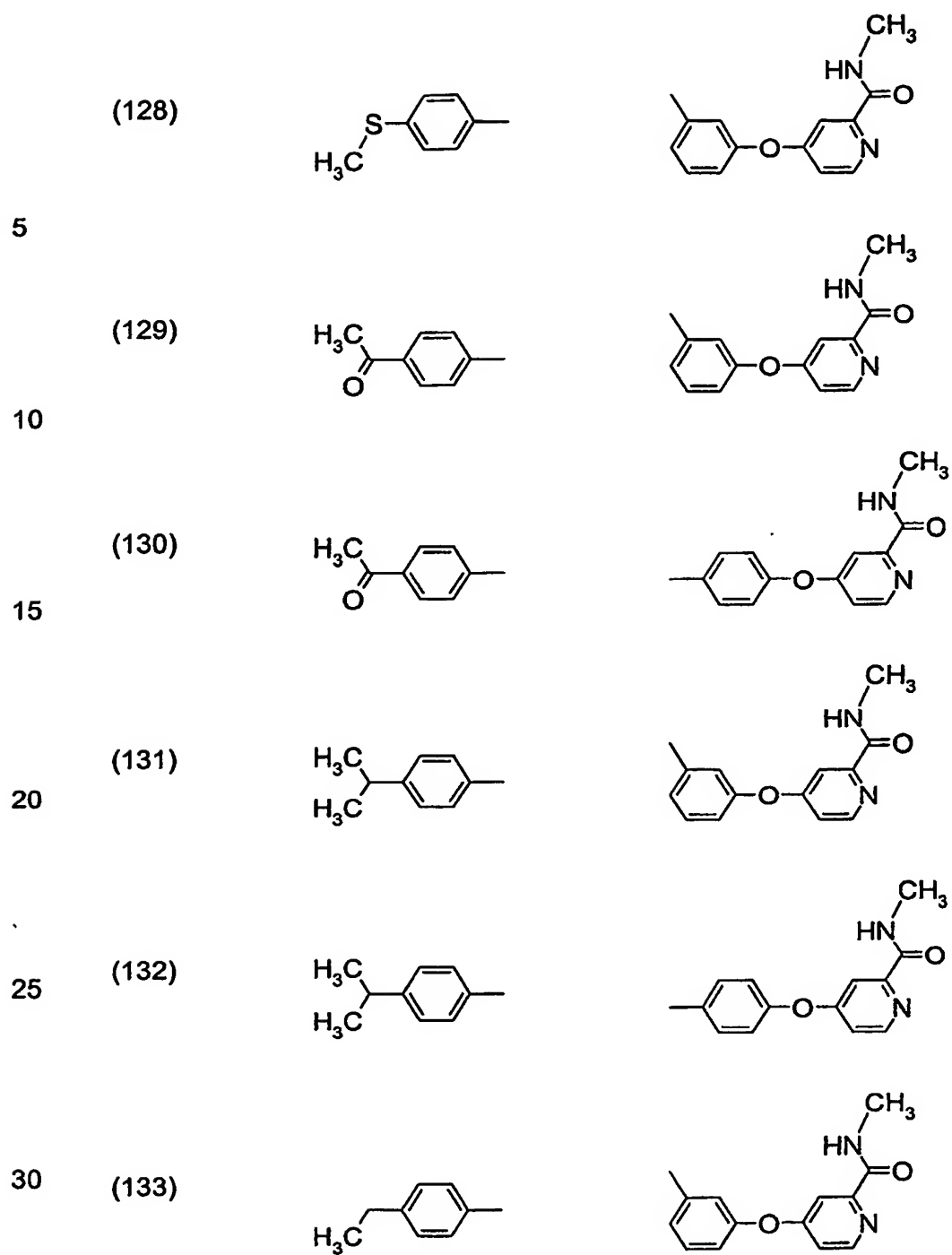
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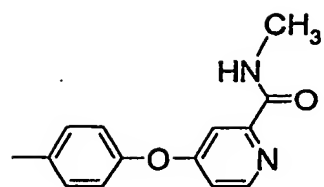
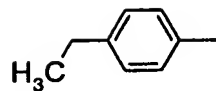


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	(119)		
25	(120)		
30	(121)		
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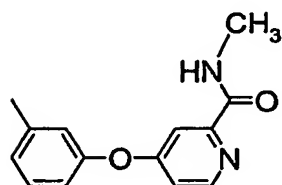
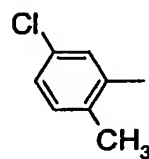


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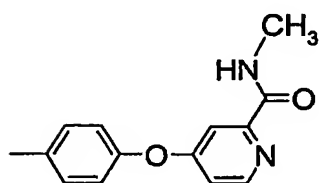
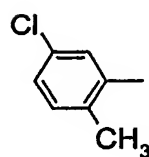
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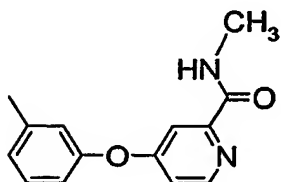
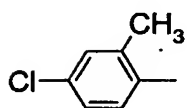
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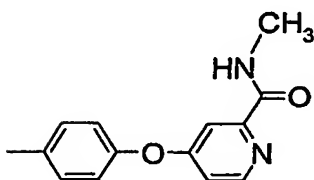
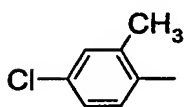
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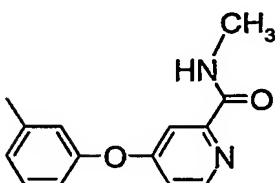
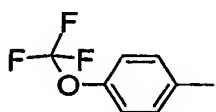
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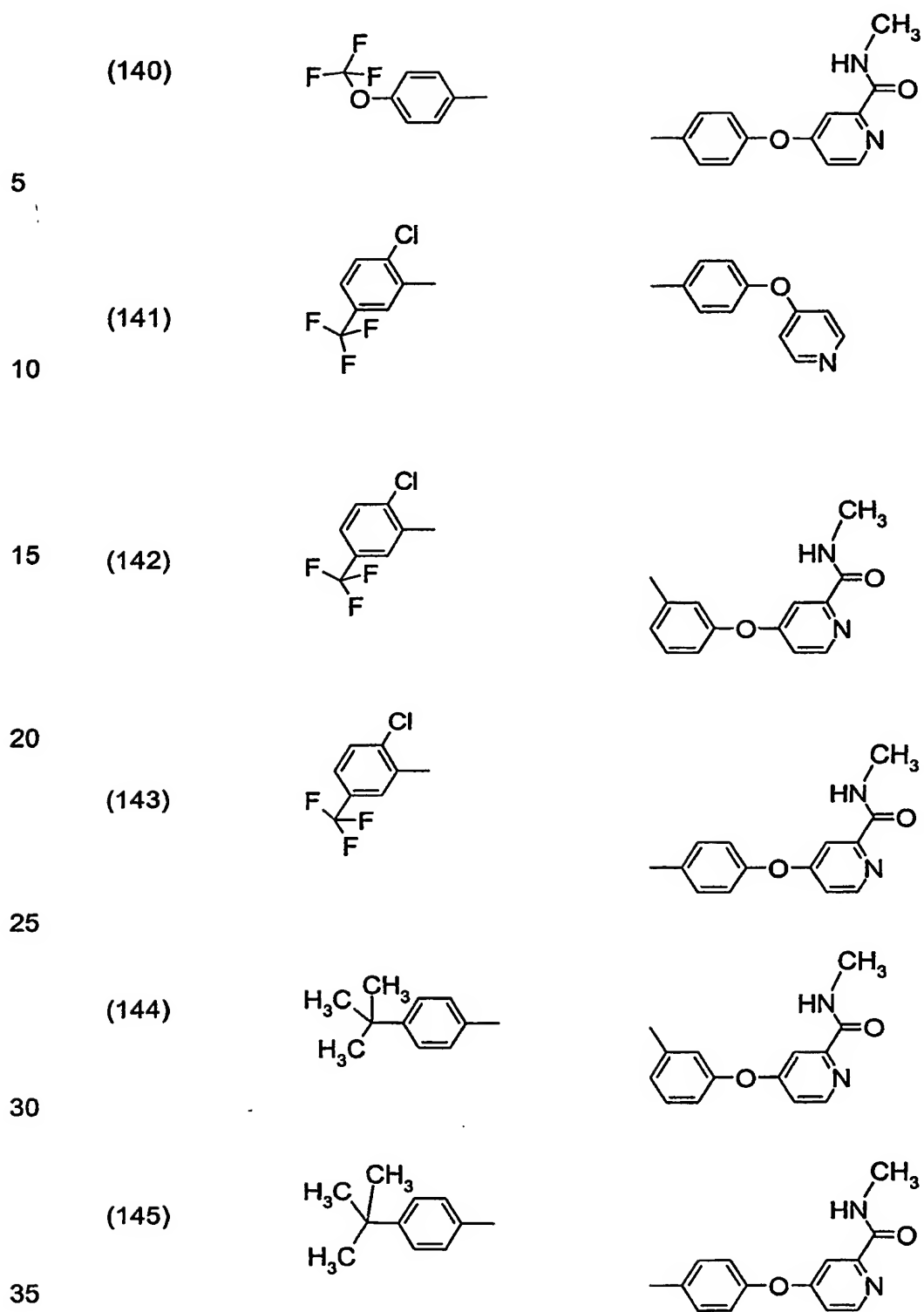
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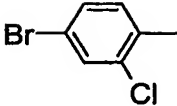
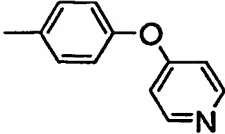
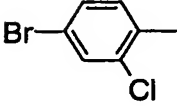
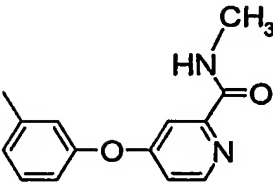
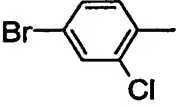
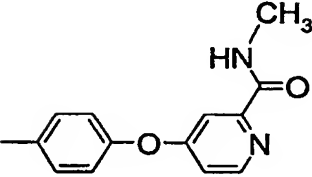
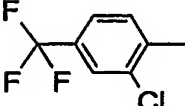
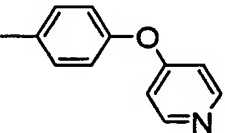
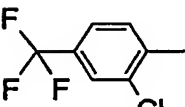
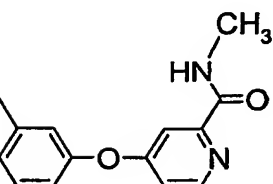
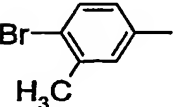
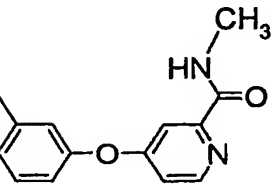
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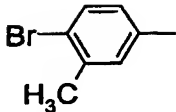
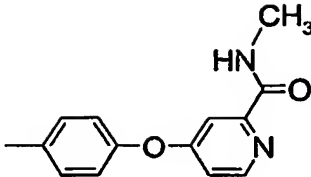
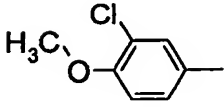
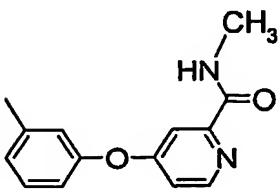
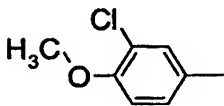
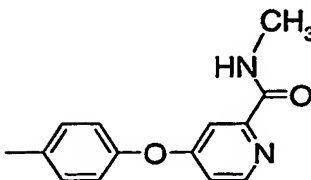
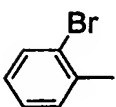
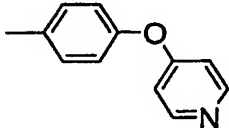
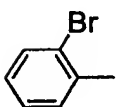
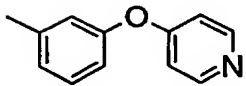
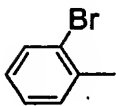
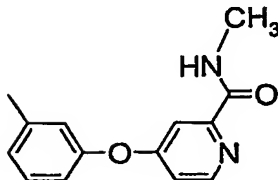


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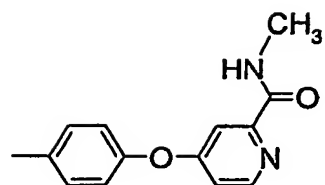
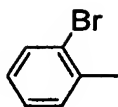
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30	(151)		
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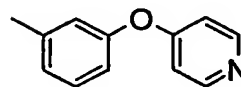
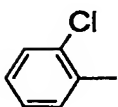
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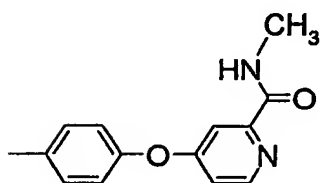
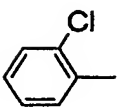
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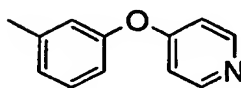
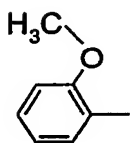
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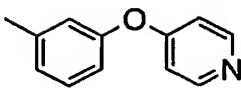
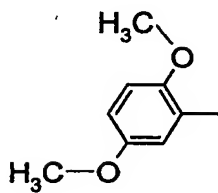
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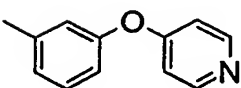
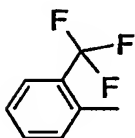
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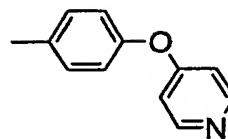
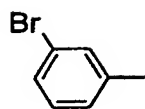
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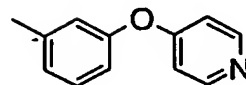
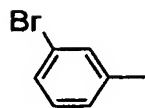
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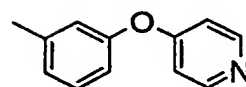
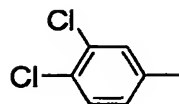
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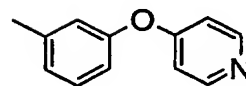
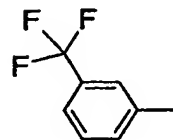
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(166)



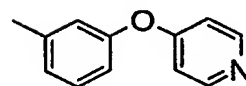
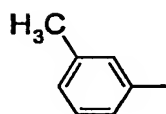
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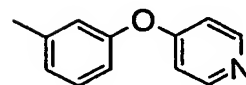
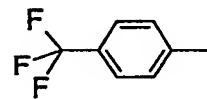
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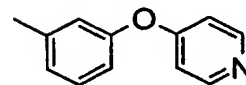
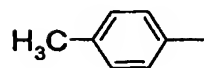
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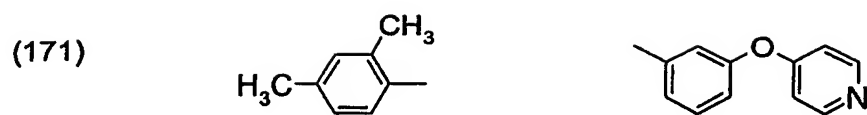


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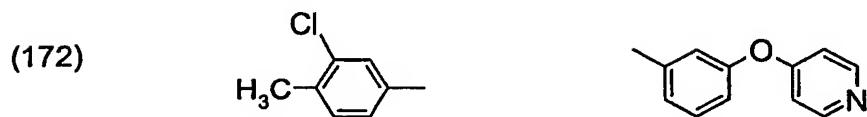
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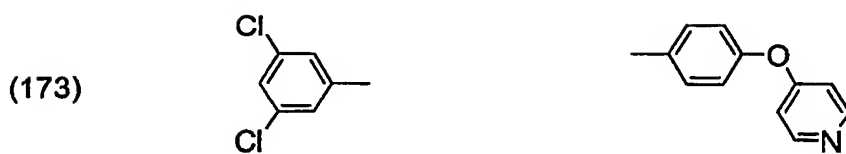
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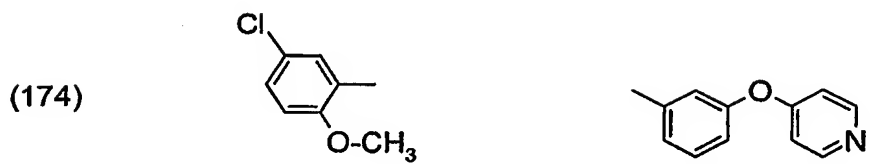
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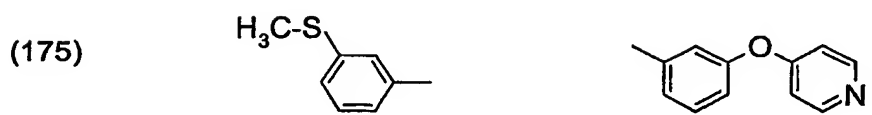
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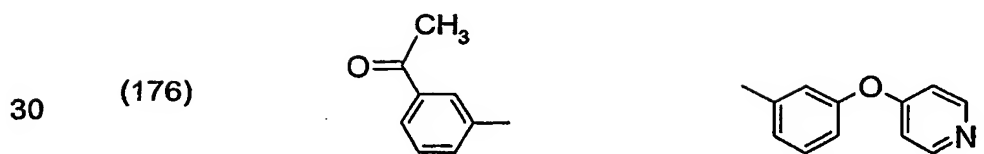
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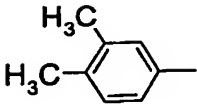
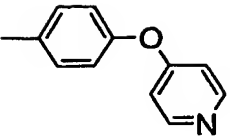
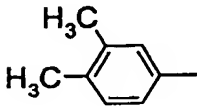
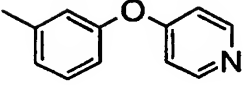
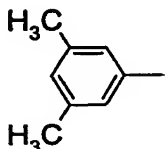
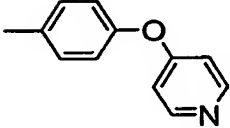
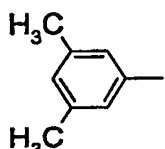
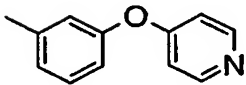
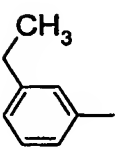
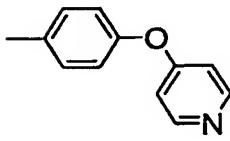
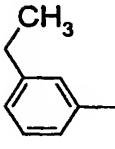
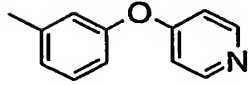


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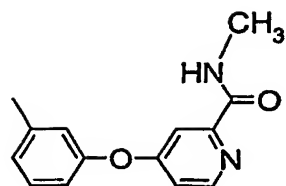
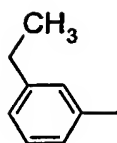


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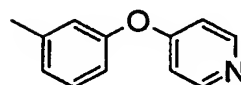
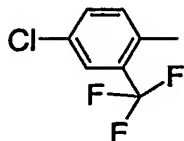
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(183)



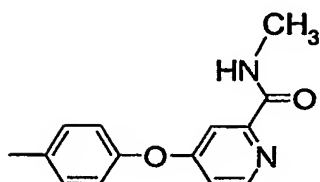
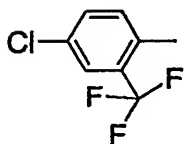
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(184)



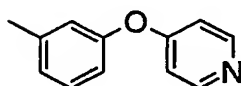
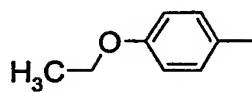
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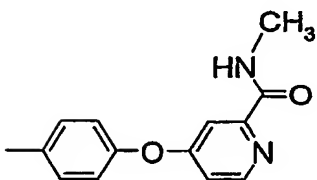
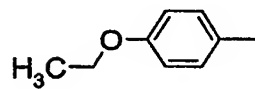
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(186)



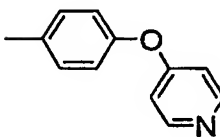
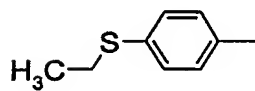
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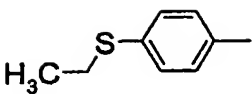
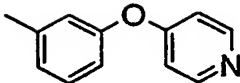
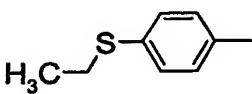
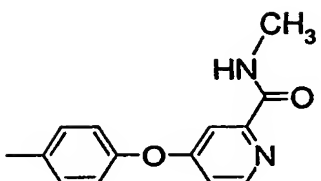
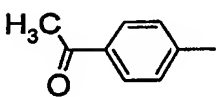
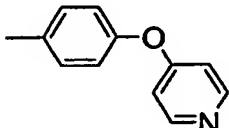
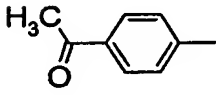
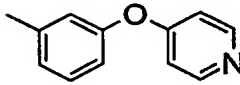
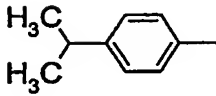
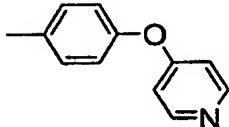
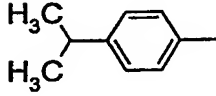
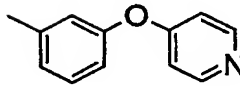
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(188)

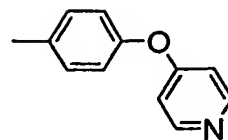
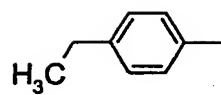


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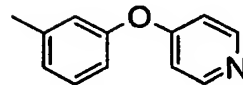
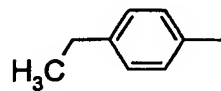
(189)		
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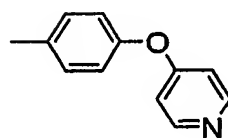
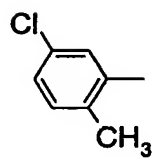
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(196)



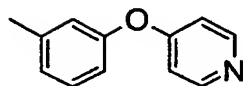
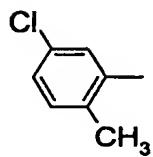
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(197)



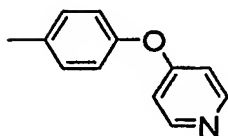
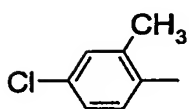
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(198)



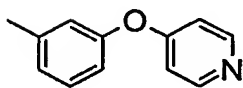
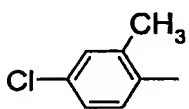
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(199)



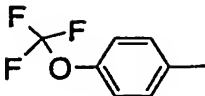
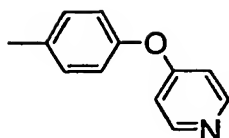
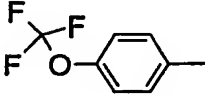
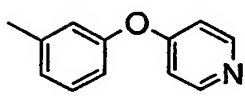
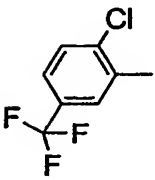
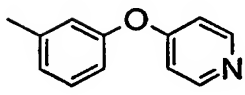
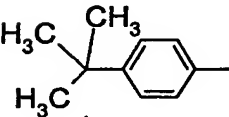
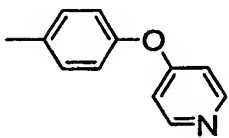
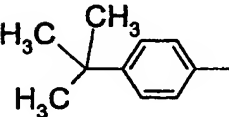
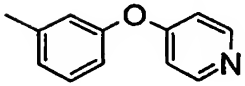
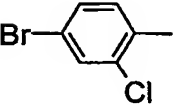
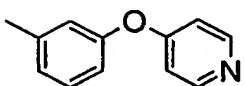
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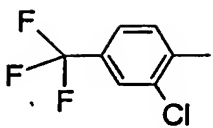
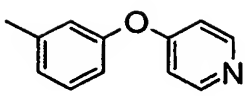
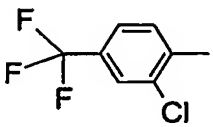
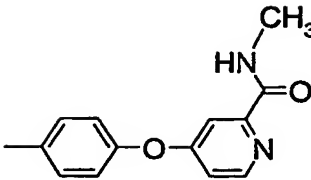
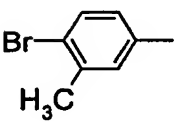
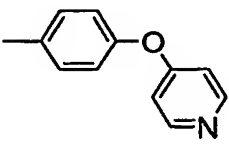
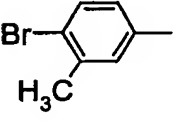
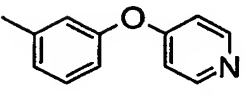
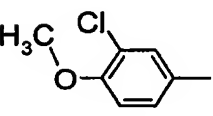
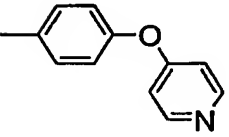
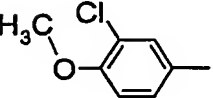
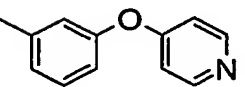
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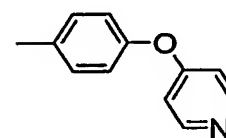
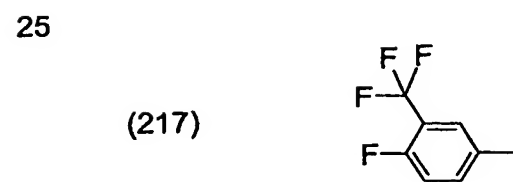
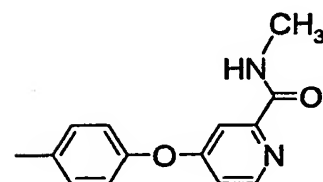
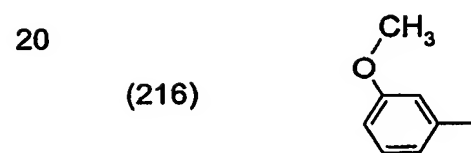
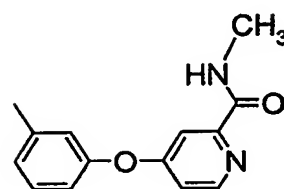
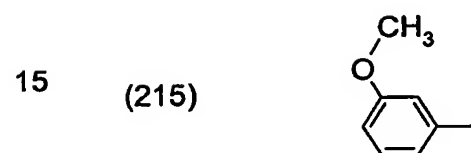
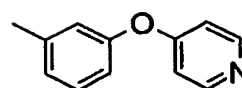
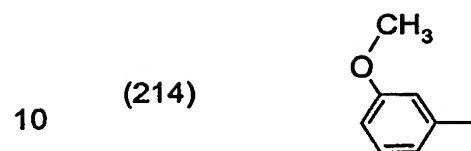
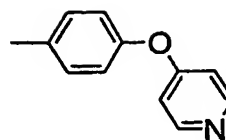
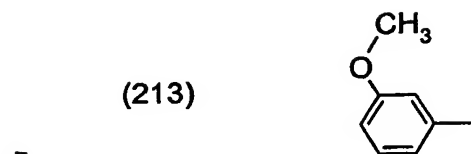


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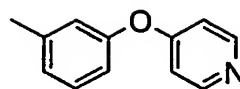
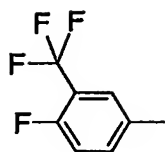
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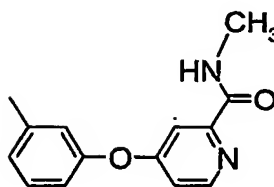
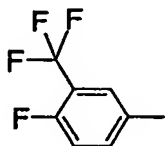
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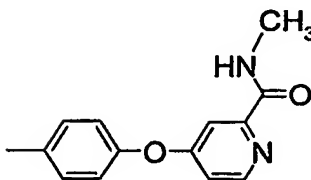
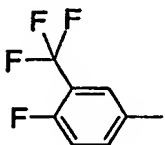
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(219)



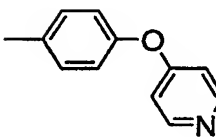
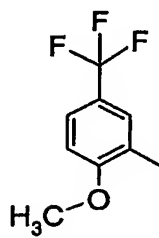
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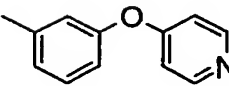
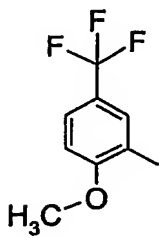
(221)



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(222)

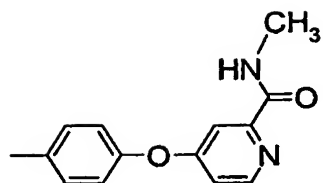
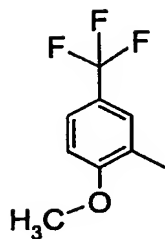


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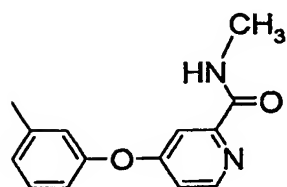
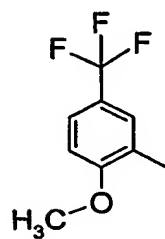
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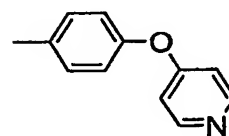
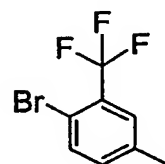
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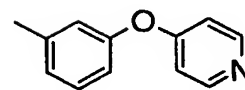
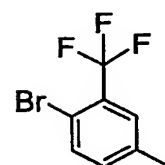
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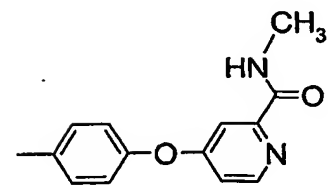
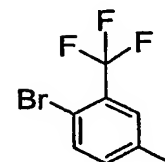
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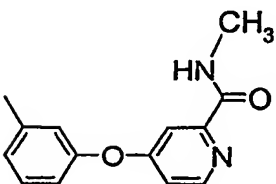
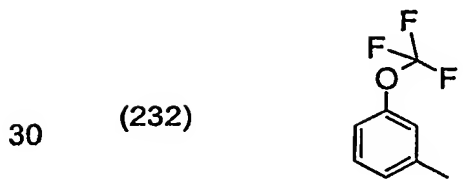
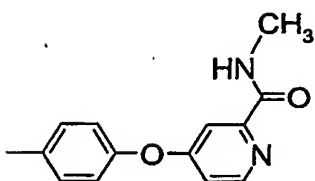
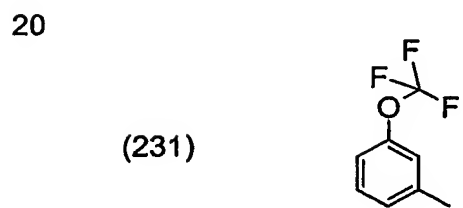
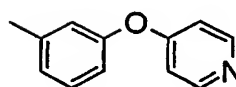
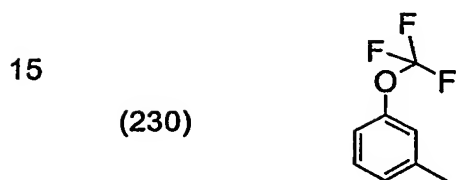
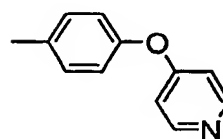
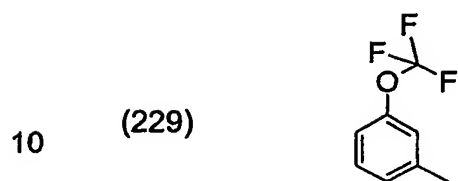
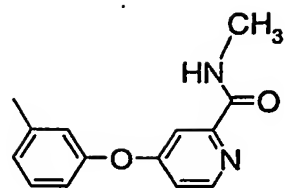
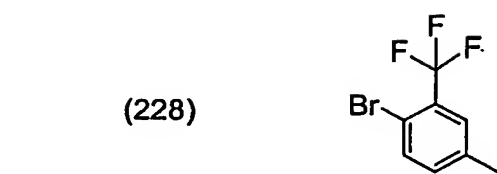


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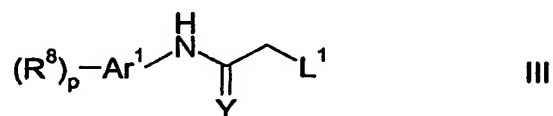


The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

5 Another aspect of the invention relates to a method for producing compounds of formula II, characterised in that

a) A compound of formula III

10



wherein

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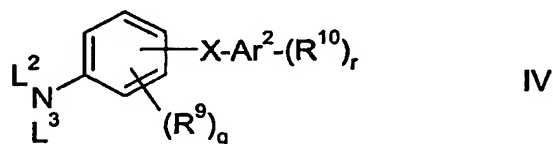
L^1 is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and R^8 , p, Ar^1 , Y are as defined above and below,

is reacted

20

b) with a compound of formula IV,

25



wherein

30

L^2 , L^3 are independently from one another H or a metal ion, and R^9 , q, X, Ar^2 , R^{10} and r are as defined above and below,

and optionally

35

- d) isolating and/or treating the compound of formula II obtained by said reaction with an acid, to obtain the salt thereof.

5 The compounds of the formula I and preferably the compounds of the formula II and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants
10 which are known per se, but are not mentioned here in greater detail.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I or II, respectively. On the other
15 hand, it is possible to carry out the reaction stepwise.

The compounds of the formula I and especially the compounds of formula II can preferably be obtained by reacting compounds of the formula III with compounds of the formula IV.
20

In detail, the reaction of the compounds of the formula III with the compounds of the formula IV is carried out in the presence or absence of a preferably inert solvent at temperatures between about -20° and about 200° , preferably between 0° and 150° and especially between room temperature (25°) and 120° . In many cases, it is advantageous to combine
25 one compound of formula III with one compound of formula IV at the lower end of the given temperature range, preferably between -20° and 75° , more preferred between 0° and 60° and especially between 10° and 40° , for example at about room temperature, and heat the mixture up to a
30 temperature at the upper end of the given temperature range, preferably between 80° and 180° , more preferred between 90° and 150° and especially between 95° and 120° , for example at about 100° or at about 110° .

35

In general, the compounds of formula III and/or formula IV are new. In any case, they can be prepared according to methods known in the art, for example according to the procedures described in WO 00/42012 or analogong to those procedures.

5 In the compounds of formula III, L^1 is preferably Cl, Br, I, OH, a reactive derivatized OH-moiety, especially a reactive esterified OH-moiety, for example an alkylsulfonyloxy-moiety comprising 1 to 6 carbon atoms (preferably methylsulfonyloxy) or and arylsulfonyloxy-moiety comprising 6
10 diazonium moiety, more preferred Cl, Br or I and even more preferred Cl.

In the compounds of formula IV, L^2 and/or L^3 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of
15 alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na K are especially preferred. In case of multi-valent metal ions, the metal ions and the compounds of formula IV form a complex containing one or more
20 compounds of formula IV and one or more metal ions wherein the ratiobetween compounds of formula IV and metal ions is depending on the valency of the metal ion(s) according to the rules of stichiometry and/or electroneutrality.

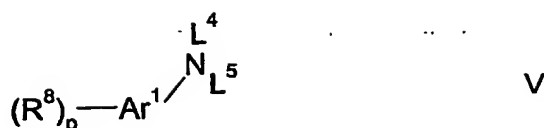
25 The reaction between the compounds of formula III and compounds of formula IV is preferably carried out in the presence of an acid binding means, for example one or more bases. Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and
30 alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is
35

higher than the highest reaction temperature employed during the reaction. Especially preferred as organic base is diisopropyl ethyl amine.

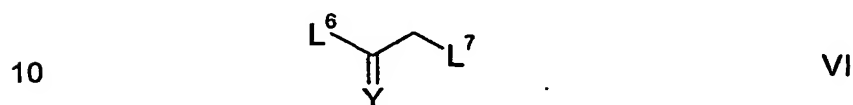
5 Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 24 hrs, preferably 30 min and 12 hrs and especially between 45 min and 8 hrs, for example
10 about 1 h, about 2 hrs, about 4 hrs or about 6 hrs.

Preferably, the reaction of the compounds of the formula III with the compounds of the formula IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions.
15 Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl
20 ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide
25 (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are amides, especially dimethylform-
30 amide (DMF).

The compounds of formula III can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by reacting a compound of formula V
35



5 wherein R^8 , p , and Ar^1 are as defined above/below and L^4 and L^5 are selected independently from each other from the meanings given for L^2 and L^3 and more preferred are hydrogen, with a compound of formula VI



10 wherein Y is as defined above/below and L^6 and L^7 are selected independently from each other from the meanings given for L^1 . Preferably, L^6 and/or L^7 are halogen. More preferred, both L^6 and L^7 are independently selected from the group consisting of Cl, Br and I. Especially preferred, both L^6 and L^7 are Cl.

15 Some of the starting materials of the formula V and/or the formula VI are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

20 Suitable reaction conditions for carrying out reaction of compounds of formula V with compounds of formula VI are known in the art. In detail, the reaction of the compounds of the formula V with the compounds of the formula VI is carried out in the presence or absence of a preferably inert solvent at temperatures between about -40° and about 180° , preferably between -20°C and 100° and especially between -10° and 50° , for example at about 0° and/or about room temperature (25°). In many cases, it is advantageous to combine one compound of formula V with one compound of formula VI at the lower end of the given temperature range, preferably between -20° and 40° , more preferred between -10° and 20° and especially between -5° and 10° , for example at about 0° , and heat the mixture up to a temperature at the upper end of the given temperature range, preferably between 20° and 150° , more preferred between 20° and

100° and especially between 20° and 50°, for example at about room temperature.

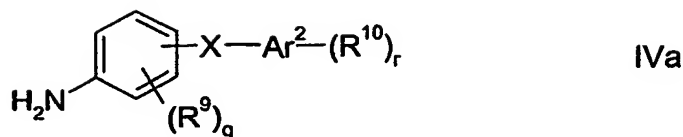
5 The reaction between compounds of formula V and compounds of formula VI is preferably carried out in the presence of an acid binding means, for example one or more bases. Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. 10 Examples for organic bases are triethyl amine, diisopropyl ethal amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. 15 Especially preferred as organic base is pyridine.

The reaction between compounds of formula V and compounds of formula VI can be carried out in the presence of a suitable solvent, that is preferably inert at the chosen reaction conditions. Suitable solvents are known in the art. Examples of suitable solvents include hydrocarbons, 20 such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; nitriles, 25 such as acetonitrile; esters, such as ethyl acetate, or mixtures of the said solvents. Non-protic solvents are in general preferred.

30 If the reaction between a compound of formula V and a compound of formula VI is carried out in presence of an organic base that is liquid at the chosen reaction conditions, preferably no additional solvent is used.

The compounds of formula IV can be obtained according to methods known in the art.

35 If the compound of formula IV is a compound according to formula IVa,



5

it can be readily obtained in an advantageous manner by reacting a compound of formula VIIa,

10



wherein R^9 and q are as defined above/below,

15

with a compound of formula VIII,



20

wherein L^8 is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminum ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred H; and Ar^2 , R^{10} , r and X are as defined above/below, and especially wherein X is $(CHR^{11})_h-Q-(CHR^{12})_j$, wherein R^{11} , h and R^{12} are defined above/below, j is 0 and Q is selected from a group consisting of O, S, $N-R^{17}$, $(CHR^{18}-O)_j$, $(CHR^{18}CHR^{19}-O)_j$, $CH=N-O$, $CH=N-NR^{17}$, SO_2NR^{17} , wherein R^{17} , R^{18} and R^{19} are as defined above/below;

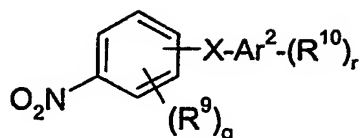
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optionally isolating the reaction product,

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and transferring the obtained reaction product of formula IX

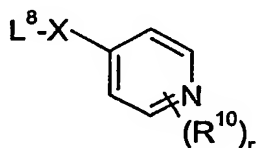
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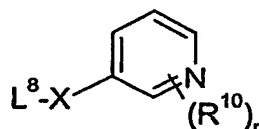
IX

5 into a compound of formula IVa, preferably by hydrogenating the
 NO₂-moiety of the compound of formula IX into a NH₂-moiety. Methods
 and reaction conditions for hydrogenating said NO₂-moiety into a NH₂-
 moiety are known in the art. In general, it is advantageous to carry out the
 hydrogenation reaction in a hydrogen atmosphere in the presence of a
 10 suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In
 general, such hydrogenation reactions are carried out in a suitable solvent.
 Suitable solvents for hydrogenation reactions are known in the art. Suitable
 solvents, for example, are alcohols, especially methanol and ethanol and
 ethers, especially THF, and mixtures thereof. In general, the hydrogenation
 15 reactions are carried out at about normal pressure or slightly elevated
 pressure, for example between normal pressure and 3 bar pressure (about
 300 kPa). The hydrogenation reaction is usually carried out in the
 temperature range between -20° and 150°, preferably 0° and 50°.

20 Ar² is preferably pyridinyl. Accordingly, the compound of formula VIII is
 preferably selected from the group consisting of formulae VIIIa and VIIIb,



VIIIa

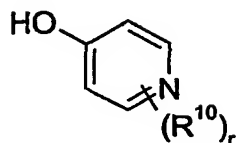


VIIIb

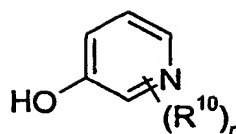
30 wherein L⁸, X, R¹⁰ and r are as defined above, and especially preferred
 from the group consisting of formulae VIIIc and VIId,

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- 100 -



VIIIc



VIId

5

wherein R^{10} and r are as defined above, or the alkaline metal salts and especially the sodium or potassium salts thereof.

10

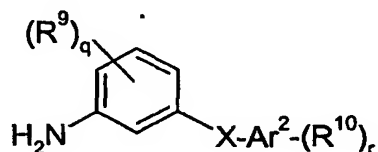
Accordingly, in formulae IVa, VIII, VIIIa, VIIIb and IX, the bridging group X is preferably O, S, OCH_2 and OCH_2CH_2 and especially is O.

In the formulae VIII, VIIIa and VIIIb, L^8 is preferably H or selected from the group consisting of Na, K and Cs and especially preferred is H.

15

In general, this reaction is advantageous to produce compounds of formula IVaa,

20



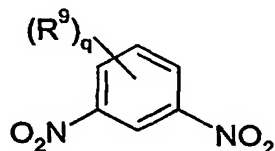
IVaa

wherein R^9 , q , X , Ar^2 , R^{10} and r are as defined above/below.

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To obtain compounds of formula IVaa, it is reasonable to employ a compound of formula VII that is selected from the compounds of formula VIIa,

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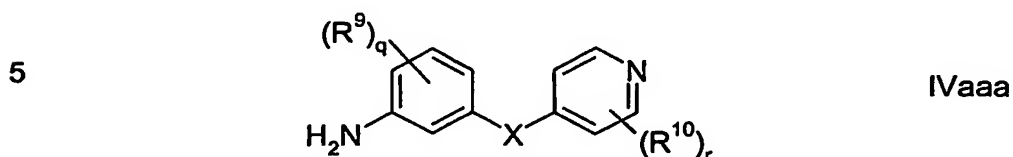


VIIa

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and proceed the reaction as described above/below.

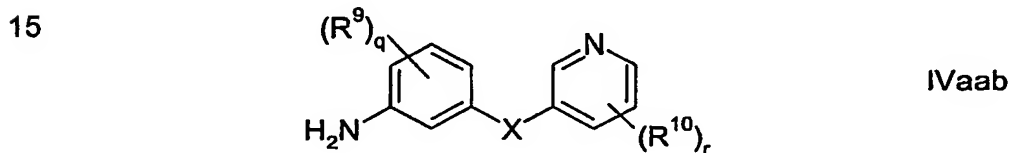
Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIa, the reaction preferably leads to compounds of formula IVaaa,



wherein R^9 , q , X , R^{10} and r are as defined above/below.

10

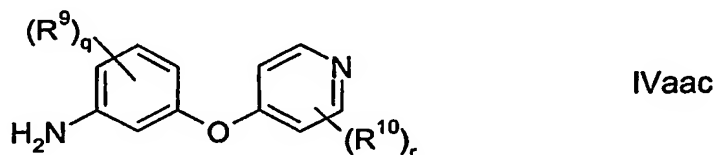
Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIb, the reaction preferably leads to compounds of formula IVaab,



20 wherein R^9 , q , X , R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIc, the reaction preferably leads to compounds of formula IVaac,

25

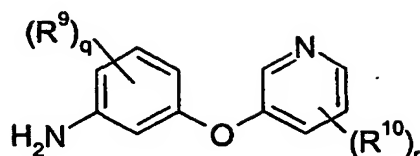


30

wherein R^9 , q , R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIa and a compound of formula VIId, the reaction preferably leads to compounds of formula

35



IVaad

5 wherein R^9 , q , R^{10} and r are as defined above/below.

Some of the starting materials of the formula VII and/or the formula VIII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

10

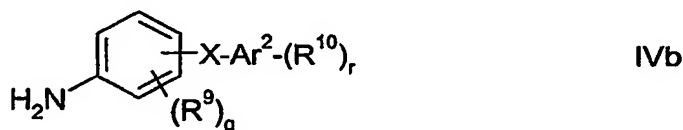
The reaction between the compound of formula VII and VIII is preferably carried out in the temperature range between 0° and 250° , more preferred room temperature and 200° , for example at about 120° , at about 150° or at about 180° . Reaction times depend on the respective reactants and the
 15 respective reaction temperature, but generally lie in the range between 30 min and 36 hrs, preferably 3 hrs and 24 hrs, more preferably 8 hrs and 20 hrs for example about 10 hrs, about 16 hrs or about 18 hrs.

The reaction can be carried out in the absence of solvent or preferably in
 20 the presence of an solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high boiling aliphatic hydrocarbons, high boiling aromatic carbons, for example toluene, xylenes, high boiling chlorinated hydrocarbons, such as
 25 trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; high boiling ethers, such as ethylene glycol and propylene glycols; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); sulfoxides,
 30 such as dimethyl sulfoxide (DMSO); or mixtures of the said solvents. Preferred are amides, especially dimethylformamide (DMF).

Preferably, the reaction is carried out in the presence of a base. Suitable bases are known in the art. Preferred bases are organic bases and
 35 especially inorganic bases. Examples for inorganic bases are alkaline or

alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Preferred inorganic bases are K_2CO_3 , Na_2CO_3 , $MgCO_3$, $CaCO_3$, NaOH and KOH, especially preferred is K_2CO_3 . Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction.

Alternatively, if the compound of formula IV is a compound according to formula IVb,

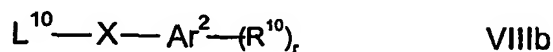


it can be readily obtained in an advantageous manner by reacting a compound of formula VIIb,



wherein R^9 and q are as defined above/below and wherein L^9 is selected independently from the meanings given for L^1 . Preferably, L^9 is halogen. More preferred, L^9 is selected from the group consisting of Cl, Br and I. Especially preferred, L^9 is Cl.

with a compound of formula VIIIb,



wherein L^{10} is H or a metal ion, preferably a metal ion, more preferred a metal ion selected from the group consisting of alkaline metal ions,

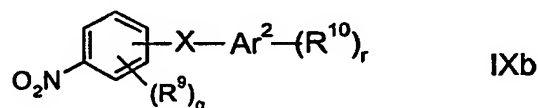
alkaline-earth metal ions and aluminium ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred; and Ar^2 , R^{10} , r and X are as defined above/below, and especially wherein X is $(CHR^{11})_h-Q-(CHR^{12})_i$, $CH=N-O$, $CH=N-NR^{17}$, SO_2NR^{17} , wherein R^{17} , R^{18} and R^{19} are as defined above/below;

5

optionally isolating the reaction product,

and transferring the obtained reaction product of formula IXb

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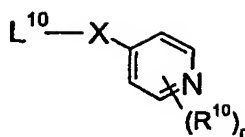
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into a compound of formula Iva, preferably by hydrogenating the NO_2 -moiety of the compound of formula IX into a NH_2 -moiety. Methods and reaction conditions for hydrogenating said NO_2 -moiety into a NH_2 -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol, ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150° , preferably 0° and 50° .

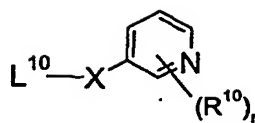
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Ar^2 is preferably pyridinyl. Accordingly, the compound of formula VIIIb is preferably selected from the group consisting of formulae VIIIe and VIII f,

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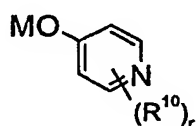
VIIIe



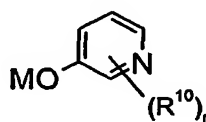
VIIIIf

5

wherein L^{10} , X, R^{10} and r are as defined above, and especially preferred from the group consisting of formulae VIIIg and VIIIh,



VIIIg



VIIIh

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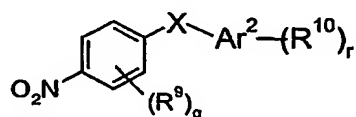
wherein R^{10} and r are as defined above, and wherein M is an alkaline metal ion and especially sodium or potassium, or the corresponding alcohols thereof.

20

Accordingly, in formulae IVb, VIIIb, VIIIe, VIIIIf and IXb, the bridging group X is preferably O, S, OCH_2 and OCH_2CH_2 and especially is O.

In general, this alternative reaction is advantageous to produce compounds of formula IVbb,

25



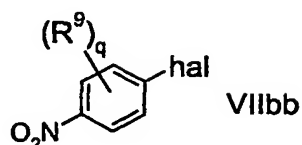
IVbb

wherein R^9 , q, X, Ar^2 , R^{10} and r are as defined above/below.

30

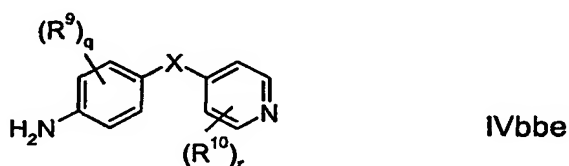
To obtain compounds of formula IVbb, it is reasonable to employ a compound of formula VIIb that is selected from the compounds of formula VIIbb,

35



5 wherein hal is as defined above/below and especially is Cl, and proceed the alternative reaction as described above/below.

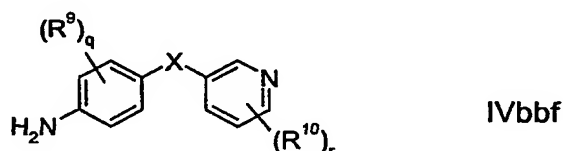
Accordingly, by starting from a compound a formula VIIbb and a
compound of formula VIIe, the reaction preferably leads to compounds of
10 formula IVbbe,



15

wherein R^9 , q, X, R^{10} and r are as defined above/below.

20 Accordingly, by starting from a compound of formula VIIbb and a compound of formula VIIIf, the reaction preferably leads to compounds of formula IVbbf,

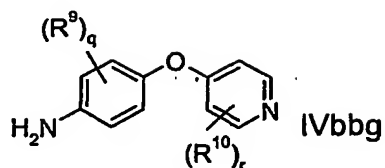


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wherein R^9 , q, X, R^{10} and r are as defined above/below.

30 Accordingly, by starting from a compound of formula VIIbb and a compound of formula VIIIg, the reaction preferably leads to compounds of formula IVbbg,

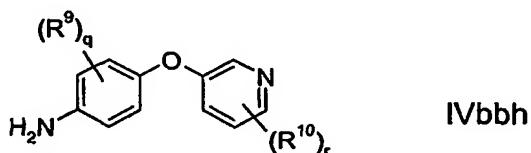
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5 wherein R^9 , q , R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIb and a compound of formula VIIIh, the reaction preferably leads to compounds of formula IVbbh,

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wherein R^9 , q , R^{10} and r are as defined above/below.

Some of the starting materials of the formula VIIb and/or the formula VIIIb are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

20

The reaction between the compound of formula VIIb and VIIIb is preferably carried out in the temperature range between 0° and 250° , more preferred 50° and 220° , for example at about 90° , at about 120° , at about 160° , at about 180° or at about 200° . Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 10 min and 24 hrs, preferably 30 min and 12 hrs, more preferably 1 h and 6 hrs for example about 1,5 hrs, about 3 hrs, about 4 hrs or about 5 hrs.

25

30

The reaction can be carried out in the absence or the presence of a solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high aliphatic hydrocarbons, aromatic carbons, for example toluene and xylenes, high boiling

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chlorinated hydrocarbons, such as dichloromethane, trichloromethane
trichloroethylene, tetrachloroethanes, pentachloroethanes and
hexachloroethanes; ethers, such as diethylether, tert.-butyl methyl ether,
ethylene glycol and propylene glycols; glycol ethers, such as ethylene
glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether
(diglyme); nitriles, such as acetonitrile, amides such as acetamide,
diethylacetamide or dimethylformamide (DMF); sulfoxides, such as
dimethyl sulfoxide (DMSO); or mixtures of the said solvents.

Preferably, the reaction is carried out in the presence of a catalyst.

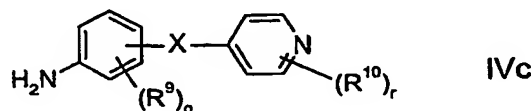
Suitable catalysts are known in the art. Preferred catalytic active metals
and especially copper.

Preferably, the reaction is carried out by heating up a reaction mixture
comprising one compound of formula VIIb and one compound of formula
VIIIb to a suitable reaction temperature, which preferably lies at the upper
end of the given temperature ranges and more preferred is in the range
between 150° and 200°, for example at about 180°, preferably in the
presence of the suitable catalyst and especially in the presence of copper.

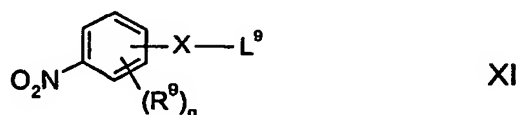
Reaction times at this temperature are preferably as given above and
especially in the range between 1 h and 5 hrs, for example about 3 hrs.

Preferably, the reaction mixture is then allowed to cool down to a
temperature in the lower range of the given temperature, more preferred to
a temperature in the range between 50° and 150°, for example to about
90°. Preferably, a suitable solvent, especially tert.-butyl methyl ether, is
then added and the reaction mixture is preferably kept at about the same
temperature for some more time, preferably for 30 min to 2 hrs and more
preferred for about one hour.

If the compound IV is a compound according to formula IVc,



it can be readily obtained in an advantageous manner by reacting a compound of formula XI

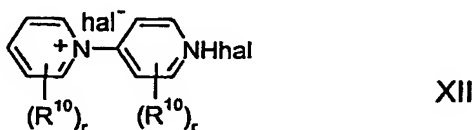


wherein L^9 is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions, especially preferred alkaline metal ions, of which Li, Na K are especially preferred, and even more preferred H; and R^9 , q and X are as defined above/below, and especially wherein X is $(CHR^{11})_h-Q-(CHR^{12})_l$, wherein R^{11} , h and R^{12} are defined above/below, j is 0 and Q is selected from a group consisting of O, S, N- R^{17} , $(CHR^{18}-O)_j$, $(CHR^{18}CHR^{19}-O)_j$, CH=B-O, CH=N-NR¹⁷, SO₂NR¹⁷, wherein R^{17} , R^{18} and R^{19} are as defined above/below;

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with a compound of formula XII,

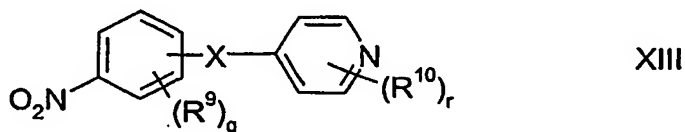


wherein hal is independently select selected from the group consisting of Cl, Br and I, the residue R^{10} are the same or different and have the meanings given above/below and preferably have both the same meaning, and the indices r are the same or different and have the meanings given above/below and preferably are the same,

25

optionally isolating the reaction product, and transferring the obtained reaction product of formula XIII

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into a compound of formula IVc, preferably by hydrogenating the NO₂-moiety of the compound of formula IX into a NH₂-moiety, for example as described above for the compound of formula IX.

5 In the compounds IVc, XII and XIII, r is preferably in each case identical and even more preferred in each case 0.

In formulae IVc, XI and XIII, the bridging group X is preferably O, S, OCH₂ and OCH₂CH₂ and especially is O.

10 In the formula XI, L⁹ is preferably H or selected from the group consisting of Na, K and Cs and especially preferred is H.

15 The reaction between the compound of formula XI and XII is preferably carried out in the temperature range between 0° and 250°, more preferred room temperature and 200°, for example at about 120°, at about 150° or at about 180°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 30 min and 24 hrs, preferably one hour and 12 hrs, for example about 2
20 hrs, about 3 hrs or about 6 hrs. The reaction can be carried out in the absence of solvent or in the presence of an solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art.

25 Some of the starting materials of the formula XI and/or the formula XII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

30 Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to evaporating a solvent, distilling,
35 crystallization, fractionised crystallization, extraction procedures, washing

procedures, digesting, filtration procedures, chromatography and chromatography by HPLC.

A base of the formula I or the formula II can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, iethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

On the other hand, if desired, the free bases of the formula I or the formula II can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

- 5 The invention relates to compounds of the formula I and of the formula II and physiologically acceptable salts and solvates thereof as medicaments.

- 10 The invention also relates to the compounds for the formula I and of the formula II and physiologically acceptable salts and solvates thereof as kinase inhibitors.

- 15 The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non- chemical methods. The invention furthermore relates to the use of the compounds of the formula II and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. In this cases, one or more
20 compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

- 25 The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, solvates of compounds of the formula I, salts of compounds of formula I, of compounds of the formula II as free bases, solvates of compounds of the formula II and salts of
30 compounds of formula II, for the production of pharmaceutical compositions and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art
35 that transfer one or more compounds according to the invention into a

dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to in invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical the active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. In this respect, active ingredients are preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds according to invention which are disclosed herein.

The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation preferably according to invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients, auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

Preferably, one or more compounds according to in invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries,

adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to methods known in the art, for example as described below:

- 5 tablets mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression
- 10 capsules mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules
- 15 semi-solids (ointments, gels, creams) dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty resp. aqueous phase, homogenisation (creams only)
- 20 suppositories (rectal and vaginal) dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms
- 25 aerosols: dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer
- 30 The invention thus relates to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates and especially to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula II and/or
- 35 one of its physiologically acceptable salts and/or solvates.

Preferably, the pharmaceutical compositions and/or pharmaceutical preparations according to the invention contain a therapeutic effective amount one or more compounds according to the invention. Said therapeutic effective amount of one or more of the compounds according to the invention is known to the artisan or can be easily determined by standard methods known in the art. For example, the compounds according to the invention can be administered to a patient in an analogous manner to other compounds that are effective as raf-kinase inhibitors, especially in an analog is manner to the compounds described in WO 00/42012 (Bayer). Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 and 100 mg per dose unit. The daily dose comprises preferably more than 0.001 mg, more preferred more than 0.01 milligram, even more preferred more than 0.1 mg and especially more than 1.0 mg, for example more than 2.0 mg, more than 5 mg, more than 10 mg, more than 20 mg, more than 50 mg or more than 100 mg, and preferably less than 1500 mg, more preferred less than 750 mg, even more preferred less than 500 mg, for example less than 400 mg, less than 250 mg, less than 150 mg, less than 100 mg, less than 50 mg or less than 10 mg.

The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for example by the doctor or physician which advises or attends the therapeutic treatment.

However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament

combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred.

5 These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or vaseline. Examples for 10 suitable dosage forms, which are especially suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops. Further examples for suitable dosage forms, which are especially suitable for for rectal administration are suppositories, further examples for suitable dosage forms, which are 15 especially suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection 20 preparations. The compositions and/or preparations indicated may be sterilized and/or comprise assistants, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavors and/or one or more further active ingredients, for example one or more vitamins.

25 For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO₂ or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in 30 which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

35 The compounds of the formula I and their physiologically acceptable salts and solvates and especially the compounds of formula II and their

physiologically acceptable salts and solvates can be employed for combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

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In General, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight.

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However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

15

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO₂ or chlorofluorocarbons).

20

The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

25

The compounds of the formula I according to claim 1 and/or their physiologically acceptable salts are also used in pathological processes which are maintained or propagated by angiogenesis, in particular in tumours, restenoses, diabetic retinopathy, macular degenerative disease or rheumatoid arthritis.

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Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given

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compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

5 For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according to the invention, particularly other anti-metastatic, antitumor or anti-angiogenic agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc. Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-
10 C, BICNU, busulfan, CNNU, cisplatin, cytoxan, daunorubicin, DTIC, 5-FU, hydrea, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen mustard, velban, vincristine, vinblastine, VP-16, carboplatin, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

15 The compounds of the invention have been shown to have antiproliferative effect in an in vivo xenograft tumor model. The subject compounds are administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a
20 lymphoproliferative disorder, to inhibit graft rejection, or neurological damage due to tissue repair, etc. The present compounds are useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is used to refer to both prevention of disease, and treatment of pre-existing conditions. The prevention of proliferation is accomplished by
25 administration of the subject compounds prior to development of overt disease, e.g., to prevent the regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc. Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

30 The host, or patient, may be from any mammalian species, e.g., primate sp., particularly human; rodents, including mice, rats and hamsters; rabbits; equines, bovines, canines, felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of
35 human disease.

5 The susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to induce cell death or inhibit migration, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used. The viable cells left after treatment are then counted.

10 The dose will vary depending on the specific compound utilized, specific disorder, patient status, etc. Typically a therapeutic dose will be sufficient to substantially decrease the undesirable cell population in the targeted tissue, while maintaining patient viability. Treatment will generally be continued until there is a substantial reduction, e.g., at least about 50 %, decrease in the cell burden, and may be continued until there are essentially none of the undesirable cells detected in the body.

15 The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

20 The compounds also find use in the specific inhibition of signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling pathways, for example
25 to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle regulation or in response to
30 extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include psoriasis, arthritis, inflammation, endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins preferably raf kinases, e.g., there is a decrease in
35 the phosphorylation of a specific substrate in the presence of the

compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.

5 There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of a variety of conditions where there is proliferation and/or migration of smooth muscle cells, and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that vessel, e.g.,
10 neointimal occlusive lesions. Occlusive vascular conditions of interest include atherosclerosis, graft coronary vascular disease after transplantation, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

15 Diseases where there is hyperproliferation and tissue remodelling or repair or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds. The growth and proliferation of neural cells is also of interest.

20 Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-modulate cell death (apoptosis) and activate angiogenesis to product a
25 tumor neovasculature.

Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial, stomach, dysplastic oral mucosa, polyposis, invasive oral
30 cancer, non-small cell lung carcinoma, transitional and squamous cell urinary carcinoma etc.; neurological malignancies; e.g. neuroblastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis fungoides, non-MF cutaneous T-cell-
35 lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid

hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, etc.; and the like.

5 Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas, etc. Some cancers of particular interest include breast cancers, which are primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized through the wall of the duct and invaded the fatty tissue of the breast. Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has the potential metastasize elsewhere in the body. About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

15 Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer. Epidermoid carcinoma (also called squamous cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

25 Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the

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primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

5

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocytes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

10

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

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Accordingly, the use of the compounds according to the invention in the treatment of Hyperproliferative disorders is a subject of the instant invention.

25

Accordingly, the use of the compounds according to the invention for producing a medicament for the treatment of hyperproliferative disorders is a subject of the instant invention

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Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated NaHCO₃ solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium

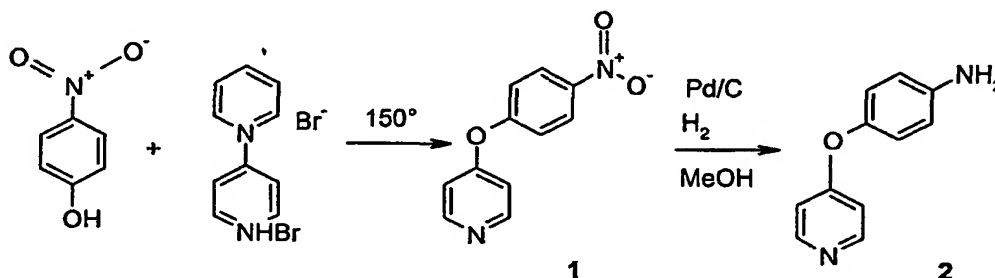
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sulfate and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallization.

The present invention relates to glycinamide derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

Examples

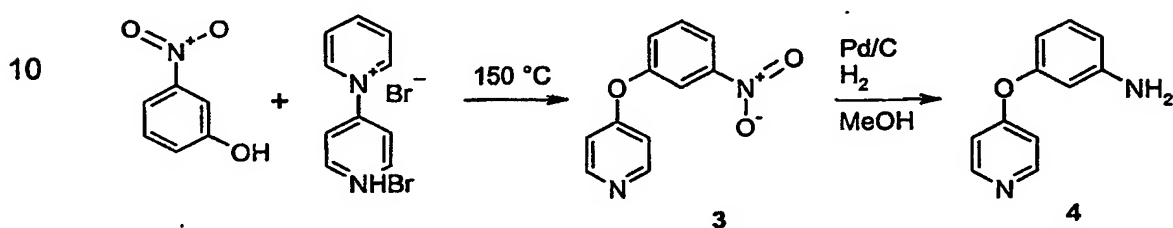
4-(4-Pyridinyloxy)-phenylamine (2)



- a) In a reaction apparatus equipped with a stirring means and a cooler, 195 g (1.4 mol) 4-nitrophenol and 445.2 g (1.4 mol) bipyridin are slowly heated up to a temperature of 150 °C under agitation. After three hours of stirring at 150 °C, the hot reaction mixture is poured into ice-cool water, acidified with hydrochloric acid and washed with methyl tert.-butyl ether (2 x 3 l). The organic phase is turned basic (pH about 12) by addition of concentrated caustic soda solution and extracted with methyl tert.-butyl ether (2 x 3 l). The combined organic phases are washed with water (4 x 1 l), dried over Na₂SO₄, filtered and evaporated. The residue is dissolved in 100 ml ether, cooled in an ice bath and caused to crystallize by addition of petroleum ether (200 ml). The crystalline residue is collected by suction and dried in vacuum to yield 75 g (25 %) brownish crystals of 1.

- b) Compound 1 is hydrogenated with Pd/C in methanol. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with a diethyl ether/petroleum ether-mixture (2:1), filtered by suction, washed with petrol ether and dried in vacuo at 40 °C overnight to yield 50.94 g (76 %) brownish crystals of 2.

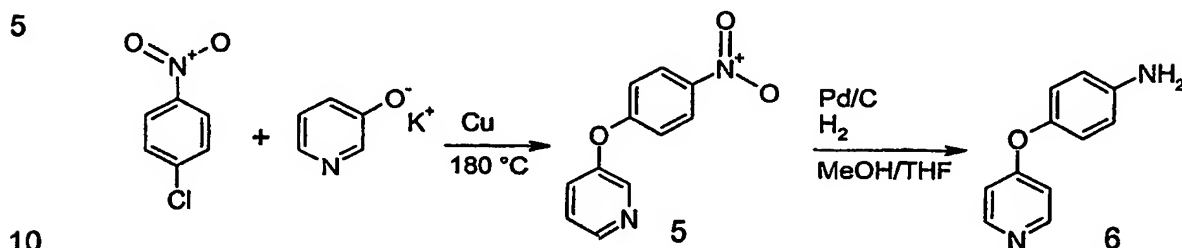
3-(4-Pyridinyloxy)-phenylamine (4)



- a) In a reaction apparatus equipped with a stirring means and a cooler, 200 g (1.44 mol/l) 3-nitrophenol and 457.93 g (1.44 mol) bipyridin are slowly heated up to a temperature of 150 °C under agitation. After three hours of stirring at 150 °C, the hot reaction mixture is poured into ice-cool water, acidified with hydrochloric acid and washed with methyl tert.-butyl ether (2 x 3 l). The organic phase is turned basic (pH about 12) by addition of concentrated caustic soda solution and extracted with methyl tert.-butyl ether (2 x 3 l). The combined organic phases are washed with water (4 x 1 l), dried over Na₂SO₄, filtered and evaporated. The residue is dissolved in 200 ml diethyl ether, treated with charcoal (20 g) for 1 h under stirring and filtered. The filtrate is evaporated to about 200 ml, cooled in a ice bath and caused to crystallize by addition of petroleum ether (500 ml). The crystalline residue is collected by suction and dried in vacuum to yield 131 g (42 %) light brownish crystals of 3.
- b) Compound 3 is hydrogenated with Pd/C in methanol. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with diethyl ether,

filtered by suction, washed with diethyl ether and dried in vacuum at 40 °C overnight to yield 98.08 g (87 %) light brownish crystals of 4.

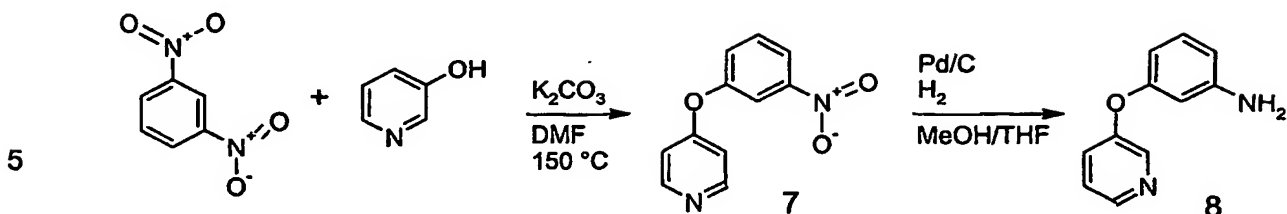
4-(3-Pyridinyloxy)-phenylamine (6)



- a) In a reaction apparatus equipped with a stirring means and a cooler, 125 g (0.94 mol) 3-hydroxypyridine, potassium salt, 300 g 1-chloronitrobenzene and 15 g copper are heated up to a temperature of 180 °C under agitation for homogenization. After three hours of stirring at 180 °C, the reaction mixture is cooled to 90 °C and methyl-tert.-butyl ether is added quickly. The resulting suspension is further stirred for 1 h, filtered by suction and the filtrate is extracted with 10 % aqueous hydrochloric acid (3 x 1 l). The resulting aqueous phase is made alkaline with ammonium hydroxide solution and extracted with ethyl acetate. The obtained organic phase is dried over Na₂SO₄, filtered and evaporated in vacuum. The residue is purified by column chromatography on silica gel (1 kg) with dichloromethane as eluent, dissolved in 10 % aqueous hydrochloric acid and extracted with ethyl acetate. The aqueous phase is made alkaline with ammonium hydroxide solution and the resulting crystalline precipitate is collected by suction, washed with little cold water and dried on air for 4 days to yield 44.7 g (22 %) brownish crystals of 5.

- b) Compound 5 is hydrogenated with Pd/C in methanol/tetrahydrofurane at room temperature. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with diethyl ether, filtered by suction, washed with diethyl ether and dried in vacuum at 40 °C overnight to yield 37.14 g (95 %) light brownish crystals of 6.

3-(Pyridinyloxy)-phenylamine (8)

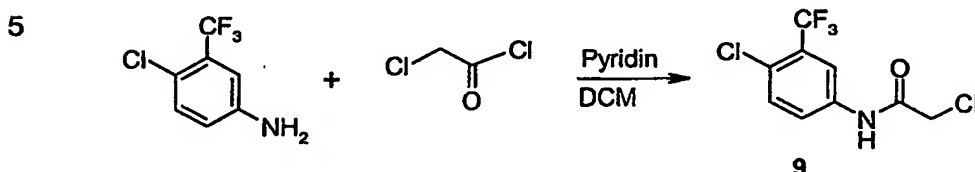


- 10 a) In a reaction apparatus equipped with this a stirring means and a cooler, 50 g (0.53 mol) 3-hydroxypyridine, 178.8 g (1.05 mol) 1,3-dinitrobenzene and 159.9 g (1.16 mol) K_2CO_3 are suspended in 1.4 l dimethyl formamide (DMF) and heated to 150 °C. After 16 hours stirring at 150 °C, the reaction mixture is cooled to room temperature and evaporated. The residue is treated with ethyl acetate (1.5 l) under stirring for 30 minutes, filtered and the filtrate is extracted with 10 % aqueous hydrochloric acid. The aqueous phase is made
- 15 alkaline with ammonium hydroxide solution and extracted with ethyl acetate. The combined organic phases are dried over Na_2SO_4 , filtered and evaporated. The residue is purified by column chromatography on silica gel (1 kg) with dichloromethane as eluent, dissolved in 10 % aqueous hydrochloric acid and extracted with ethyl
- 20 acetate. The aqueous phase is made alkaline with ammonium hydroxide solution and extracted with ethyl acetate. The combined organic phases are dried over Na_2SO_4 , filtered and evaporated to yield 98 g (and 86 %) brownish oil of 7.
- 25
- 30 b) Compound 7 is hydrogenated with Pd/C in methanol/tetrahydrofuran at room temperature. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with a diethyl ether/petroleum ether-mixture (2:1), filtered by suction, washed with petrol ether and the resulting crystals are collected. The mother liquor is evaporated to dryness and allowed to stand in the refrigerator overnight. The resulting crystals where digested with a petroleum ether/diethyl ether-mixture (9:1) and filtered by suction. The combined crystalline residues are dried in
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vacuum at 40 °C overnight to yield 77.7 g (91 %) light brownish crystals of 8.

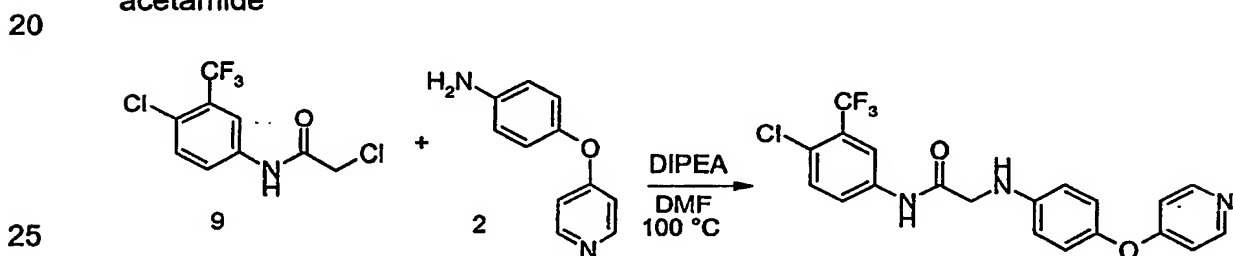
2-Chloro-N-(4-chloro-3-trifluoro methyl phenyl)-acetamide (**9**)



10 Chloroacetic acid chloride (0.69 ml; 8.44 mmol) is dropped slowly into a stirred solution of 4-chloro-3-trifluoro methyl aniline (1.5 g; 7.67 mmol) in pyridine (0.81 ml; 9.97 mmol) and dichloromethane (15 ml), cooled to 0 °C. Stirring is continued for 2 h at room temperature. The reaction mixture is deluded with dichloromethane, washed twice with 1N aqueous

15 hydrochloric acid and with water. The reaction mixture is then dried over Na₂SO₄, filtered and evaporated to yield 2.05 g (98 %) brownish solid of 9.

N-(4-Chloro-3-trifluoro methyl phenyl)-2-[4-(4-pyridinyloxy) phenyl amino]-acetamide

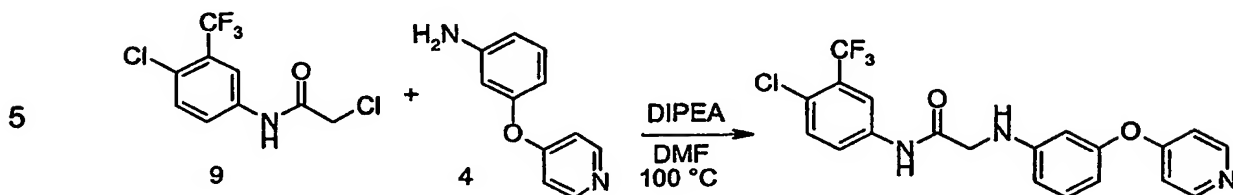


A solution of 146.1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 2 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 6 h, then evaporated and the residue is purified by

30 preparative HPLC to yield 10.7 mg (5 %) colourless solid.

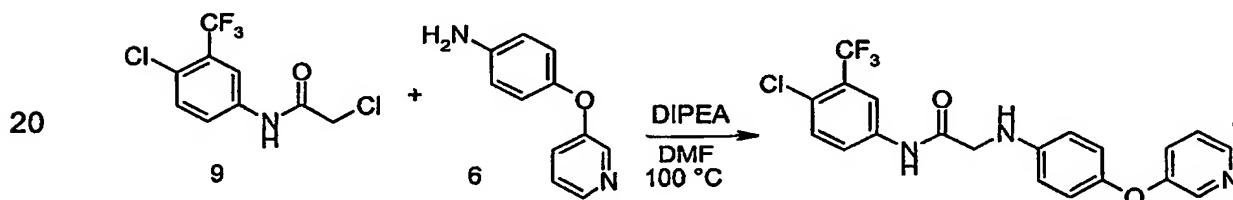
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N-(4-Chloro-3-trifluoro methyl phenyl)-2-[3-(4-pyridinyloxy) phenyl amino]-acetamide



10 A solution of 146.1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 4 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 6 h, then evaporated and the residue is purified by preparative HPLC to yield 110 mg (48 %) colourless solid.

15 N-(4-Chloro-3-trifluoro methyl phenyl)-2-[4-(3-pyridinyloxy) phenyl amino]-acetamide

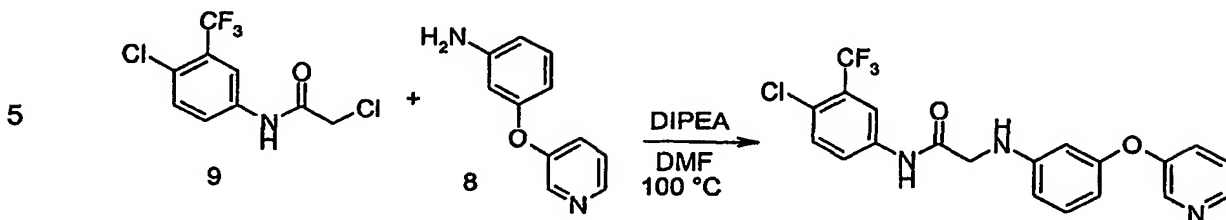


25 A solution of 146.1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 6 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 20 mg (9 %) colourless solid.

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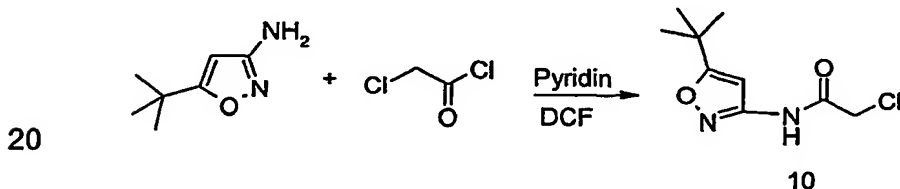
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N-(4-Chloro-3-trifluoro methyl phenyl)-2-[3-(3-pyridinyloxy) phenylamine]-
acetamide



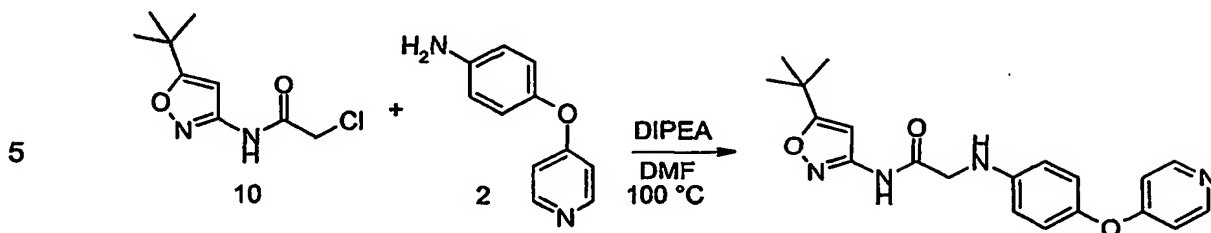
10 A solution of 146,1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 8 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 24 mg (11 %) colourless solid.

15 N-(5-t-Butyl-3-isoxazolyl)-2-chloro-acetamide



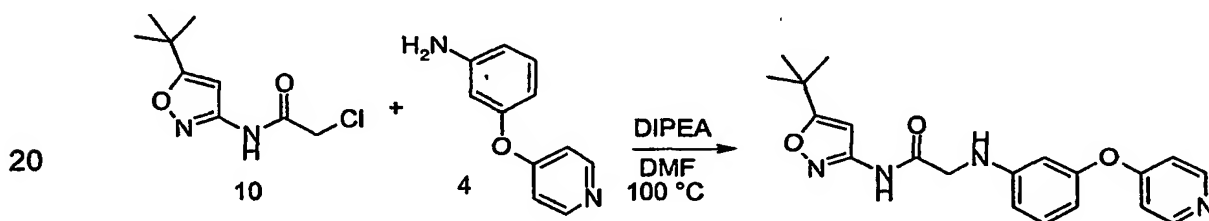
25 Chloroacetic acid chloride (0.93 ml; 11.42 mmol) is dropped slowly into a stirred solution of 5-tert-butyl-3-amino isoxazol (1.5 g; 7.67 mmol) in pyridine (1.09 ml; 13.49 mmol) and dichloromethane (20 ml), cooled to 0 °C. Stirring is continued for 2 h at room temperature. The reaction mixture is deluded with dichloromethane, washed twice with 1N aqueous hydrochloric acid, twice with an aqueous solution of NaHCO₃ and with water. The reaction mixture is then dried over Na₂SO₄, filtered and
30 evaporated to yield 2.2 g (98 %) brownish solid of 10.

N-(5-t-Butyl-3-isoxazolyl)-2-[4-(4-pyridinyloxy) phenyl amino]-acetamide



10 A solution of 58.2 mg (0.27 mmol) of compound 10 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 2 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 28 mg (29 %) colourless solid.

N-(5-t-Butyl-3-isoxazolyl)-2-[3-(4-pyridinyloxy) phenyl amino]-acetamide

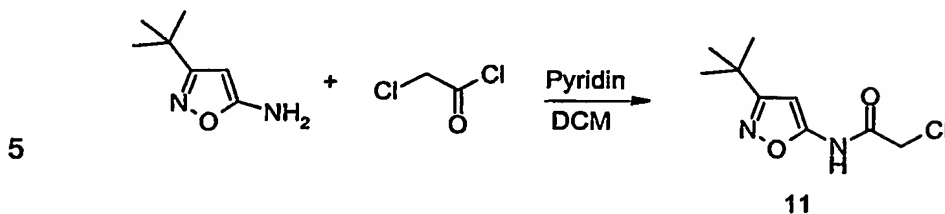


25 A solution of 58.2 mg (0.27 mmol) of compound 10 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 4 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 47 mg (48 %) colourless solid.

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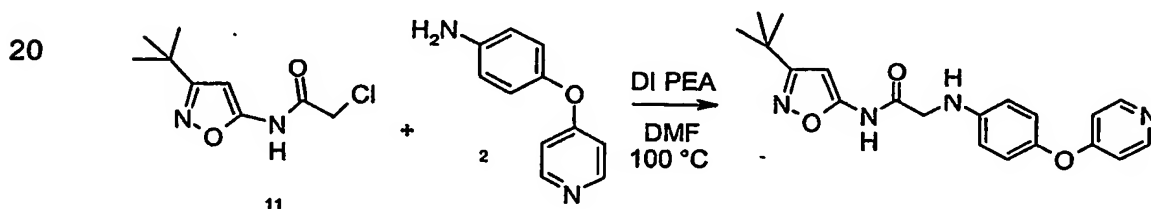
N-(3-t-Butyl-5-isoxazolyl)-2-chloro-acetamide



10 Chloroacetic acid chloride (0.25 ml; 3.14 mmol) is dropped slowly into a stirred solution of 3-t-Butyl-5-amino isoxazol (400 mg; 2.85 mmol) in pyridine (0.3 ml; 3.71 mmol) and dichloromethane (2 ml), cooled to 0 °C. Stirring is continued for 2 h at room temperature. The reaction mixture is deluded with dichloromethane, washed twice with 1N aqueous hydrochloric acid, twice with an aqueous solution of NaHCO₃ and with

15 water. The reaction mixture is then dried over Na₂SO₄, filtered and evaporated to yield 600 mg (97 %) brownish solid of 11.

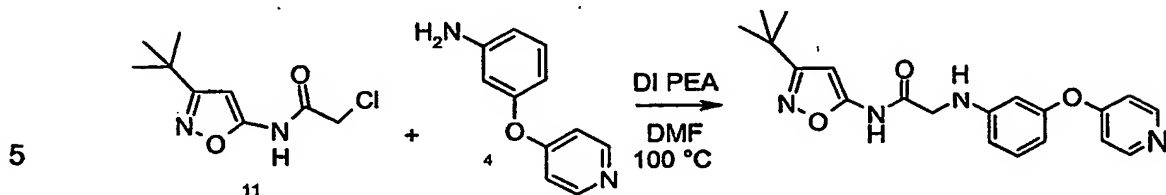
N-(3-t-Butyl-5-isoxazolyl)-2-[4-(4-pyridinyloxy)phenyl amino]-acetamide



25 A solution of 58.2 mg (0.27 mmol) of compound 11 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 2 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 2 h, then evaporated and the residue is purified by

30 preparative HPLC to yield 5.5 mg (6 %) colourless solid.

N-(3-*t*-Butyl-5-isoxazolyl)-2-[3-(4-pyridinyloxy)phenyl amino]-acetamide



10 A solution of 58.2 mg (0.27 mmol) of compound 11 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 4 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 2 h, then evaporated and the residue is purified by preparative HPLC to yield 20 mg (20 %) colourless solid.

15 The compounds (1) to (232) as described above can preferably be produced according to the procedures described herein or in an analogous manner thereof.

Example A: Injection vials

20 A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

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Example B: Suppositories

30 A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

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A solution of 1 g of an active compound of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

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Example D: Ointment

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

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Example E: Tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

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Example F: Coated tablets

Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

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Example G: Capsules

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

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Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

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Claims

1. Glycinamide derivatives of formula I

A-D-B (I)

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wherein

D is a bivalent glycinamide moiety,

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A is a substituted moiety of up to 40 carbon atoms of the formula: $-L-(M-L')_{\alpha}$, where L is a 5, 6 or 7 membered cyclic structure, preferably selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, preferably selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least to one atom, α is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L' is preferably substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$

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B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms, preferably of up to 20 carbon atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, preferably a 5- or 6-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is preferably selected from the group consisting of aryl, heteroaryl and heterocyclyl, R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

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5 R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b , where R_a and R_b are

10 a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by
15 halogen, or

20 -OSi(R_f)₃ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

25 or

30 b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by
35 halogen; or

- c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;
- where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_γ , where γ is 0-3;
- wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the groups consisting of $-CN$, $-CO_2R$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_\beta-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_\beta-$, $-(CH_2)_\beta S-$, $-(CH_2)_\beta N(R^7)-$, $-O(CH_2)_\beta-CHHal-$, $-CHal_2-$, $-S-(CH_2)-$ and $-N(R^7)(CH_2)_\beta-$ where $\beta = 1-3$, and Hal is halogen; and Ar is 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by $Z\delta_1$ wherein δ_1 is 0 to 3 and each Z is independently selected

from the group consisting -CN, -CO₂R⁷, -C(O)NR⁷R⁷,
 -C(O)-R⁷, -SR⁷, -NR⁷R⁷
 -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of
 up to 24 carbon atoms, optionally containing heteroatoms
 selected from N, S and O and optionally substituted by one
 or more substituents selected from the group consisting of
 -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂m -OR⁷, -SR⁷,
 -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, with R⁷ as defined
 above, and the salts and solvates thereof.

2. Glycinamide derivative according to claim 1, characterised in that
 each M independently from one another represents a bond OR is a
 bridging group, selected from the group consisting of (CR⁷R⁷)_n, or
 (CHR⁷)_n-Q-(CHR⁷)_i, wherein

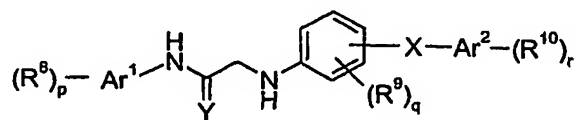
Q is selected from a group consisting of O, S, N-R⁷, (CHal₂)_j,
 (O-CHR⁷)_j, (CHR⁷-O)_j, CR⁷=CR⁷, (O-CHR⁷CHR⁷)_j,
 (CHR⁷CHR⁷-O)_j, C=O, C=S, C=NR⁷, CH(OR⁷), C(OR⁷)(OR⁷),
 C(=O)O, OC(=O), OC(=O)O, C(=O)N(R⁷)C(=O), OC(=O)N(R⁷),
 N(R⁷)C(=O)O, CH=N-NR⁷, OC(O)NR⁷, NR⁷C(O)O, S=O, SO₂,
 SO₂NR⁷ und NR⁷SO₂, wherein

R⁷ is in each case independently selected from the meanings given
 above, preferably hydrogen, halogen, alkyl, aryl, aralkyl,

h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6,
 preferably 0, 1, 2 or 3, and

j is 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3.

3. Glycinamide derivative according to claim 1 or 2, selected from the
 compounds of formula II,



II

wherein

5 Ar^1, Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two hetero atoms, independently selected from N, O und S,

10 R^8, R^9
and R^{10} are independently selected from a group consisting of H, A, cycloalkyl 3 to 7 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_2$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $CH=N-OA$, $CH_2CH=N-OA$,
15 $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^8$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^8$,
20 $(CH_2)_nN(R^8)CH_2CH_2NR^{12}R^8$, $CH=CHCOOR^{13}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$,
25 $(CH_2)_nN(CH_2COOH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

30 R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$,

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

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- A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,
- 5 Ar³, Ar⁴ are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, 10 SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,
- Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, 15 NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,
- 20 R¹⁵, R¹⁶ are independently selected from a group consisting of H, A, and (CH₂)_mAr⁵, wherein
- 25 Ar⁵ is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,
- n, m are independently of one another 0, 1, 2, 3, 4, or 5;
- 30 X represents a bond or is (CR¹¹R¹²)_n, or (CHR¹¹)_n-Q-(CHR¹²)_i, wherein
- 35 Q is selected from a group consisting of O, S, N-R¹⁷, (CHal₂)_j, (O-CHR¹⁸)_j, (CHR¹⁸-O)_j, CR¹⁸=CR¹⁹, (O-CHR¹⁸CHR¹⁹)_j, CHR¹⁸CHR¹⁹-O)_j, C=O, C=S, C=NR¹⁷, CH(OR¹⁷), C(OR¹⁷)(OR²⁰), C(=O)O, OC(=O), OC(=O)O, C(=N)(R¹⁷),

$N(R^{17})C(=O)$, $OC(=O)N(R^{17})$, $N(R^{17})C(=O)O$, $CH=N-O$,
 $CH=N-NR^{17}$, $OC(O)NR^{17}$, $NR^{17}C(O)O$, $S=O$, SO_2 , SO_2NR^{17}
 und $NR^{17}SO_2$, wherein

5 h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, and

 j is 1, 2, 3, 4, 5 or 6,

 Y is selected from O, S, NR^{21} , $C(R^{22})-NO_2$, $C(R^{22})-CN$ and
 10 $C(CN)_2$, wherein

R^{21} is independently selected from the meanings given for R^{13} ,
 R^{14} , and

R^{22} is independently selected from the meanings given for R^{11} ,
 15 R^{12} ,

 p, r are independently from one another 0, 1, 2, 3, 4 or 5,

 q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
 20

 u is 0, 1, 2 or 3, preferably 0, 1 or 2,

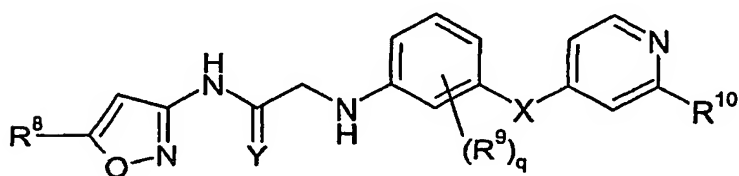
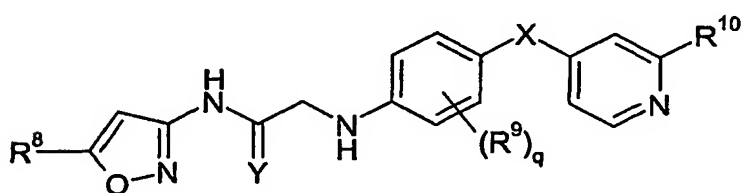
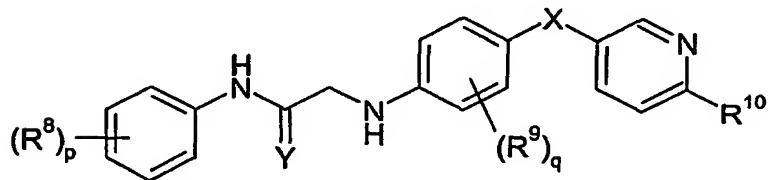
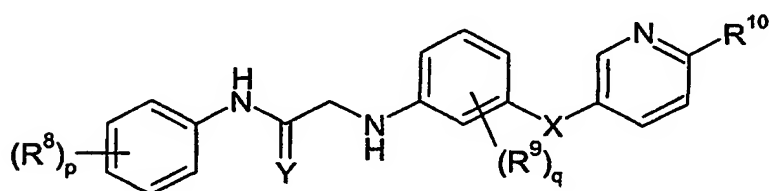
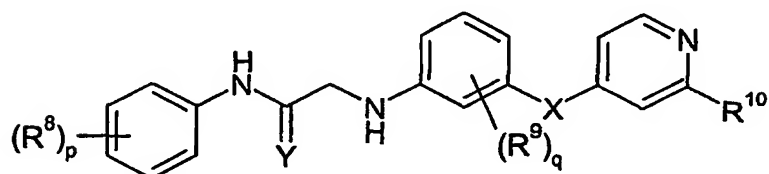
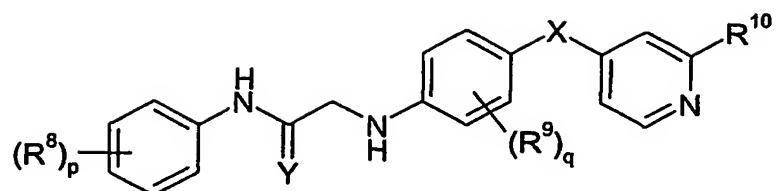
 and

25 Hal is independently selected from a group consisting of F, Cl,
 Br and I;

 and the salts and solvates thereof.

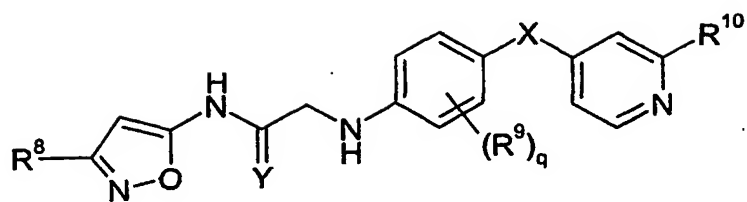
30 4. Glycinamide derivative according to one of the claims 1 to 3, selected
 from the compounds of formula IIa, IIb, IIc, IId, IIe, IIg and IIh,

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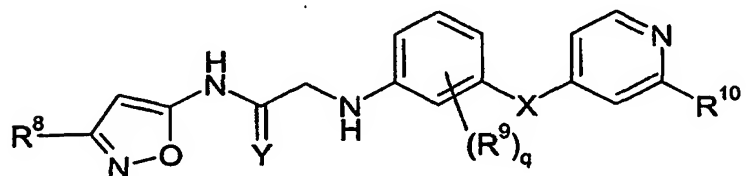


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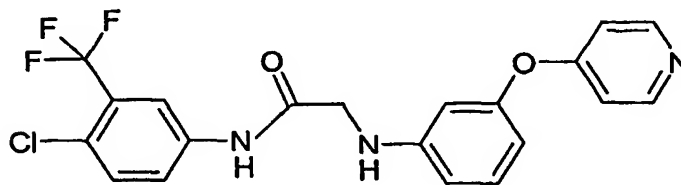
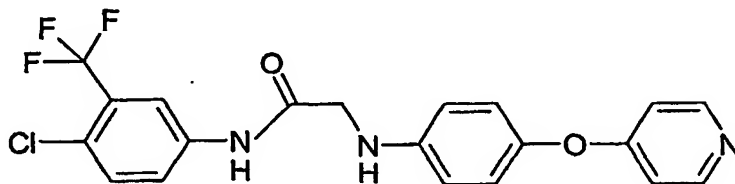
IIg



IIh

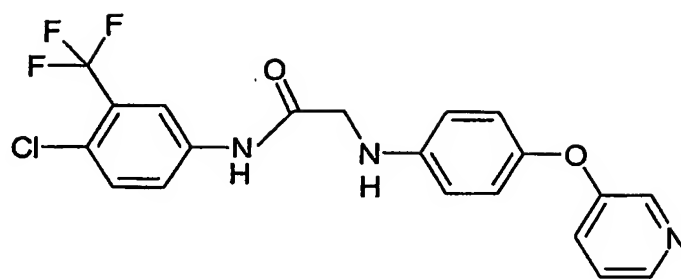
wherein R^8 , p , Y , R^9 , q and R^{10} are as defined in claim 3;
and the salts and solvates thereof.

5. Glycinamide derivative according to claim 1 or 2, selected from

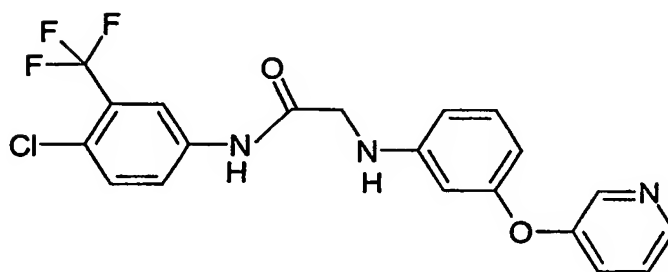


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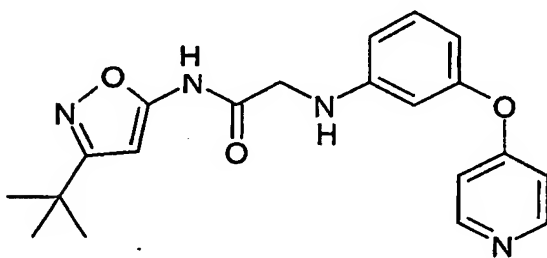


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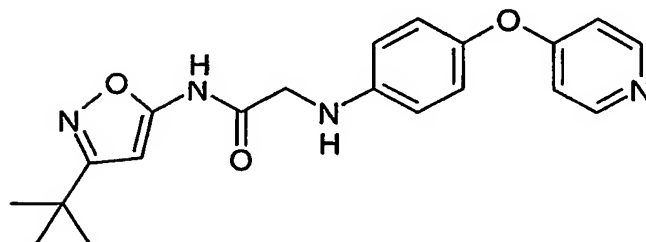
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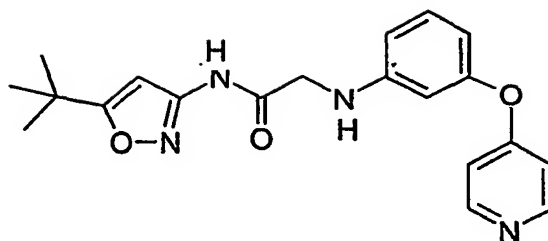


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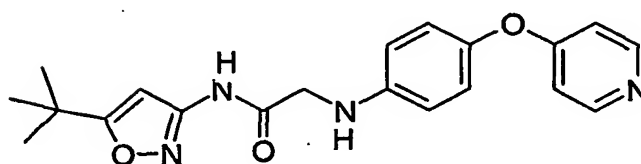
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- 15 6. Pharmaceutical composition, characterised in that it contains one or more compounds according to one of the claims 1 to 5.
- 20 7. Pharmaceutical composition according to claim 6, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants and carriers.
- 25 8. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
- 30 9. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.

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10. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
- 5 11. Use according to claim 9 or 10, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.
12. Use according to claim 9, 10 or 11, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
- 10 13. Use according to claim 9, 10, 11 or 12, characterised in that the disorder is cancer.
14. Use according to claim 9, 10, 11 or 12, characterised in that the disorder is noncancerous.
- 15 15. Use according to claim 9, 10, 11, 12 or 14, characterised in that the noncancerous disorders are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
- 20 16. Use according to one of the claims 9 to 13, characterised in that the disorders are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
- 25 17. Use of a compound according to one of the claims 1 to 5 as a raf-kinase inhibitor.
- 30 18. Use according to claim 17, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and Raf-1.
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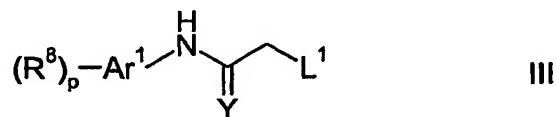
19. Method for the treatment and/or prophylaxis of disorders, characterised in that a compound according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.

5 20. Method for the treatment and/or prophylaxis of disorders according to claim 19, characterised in that the disorders are as defined in one of the claims 11 to 16.

10 21. Method for the treatment according to claim 20, characterised in that the disorders is cancerous cell growth mediated by raf-kinase.

22. Method for producing compounds of formula II, characterised in that

c) a compound of formula III

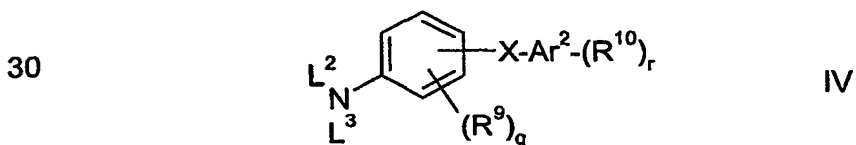


20 wherein

L^1 is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and R^8 , p, Ar^1 , Y are as defined in claim 3,

25 is reacted

d) with a compound of formula IV,



wherein

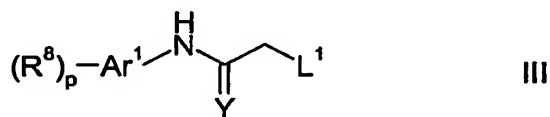
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L^2, L^3 are independently from one another H or a metal ion, and R^9, q, X, Ar^2, R^{10} and r are as defined in claim 3,

and optionally

5 isolating and/or treating the compound of formula II obtained by said reaction with an acid, to obtain the salt thereof.

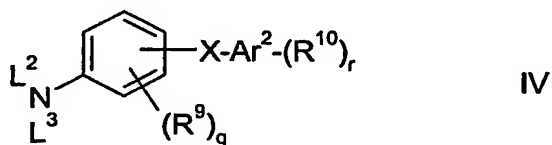
23. Compound of formula III,



wherein

L^1 is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and R^8, p, Ar^1, Y are as defined in claim 3.

24. Compound of formula IV,



wherein

L^2, L^3 are independently from one another H or a metal ion, and R^9, q, X, Ar^2, R^{10} and r are as defined in claim 3.

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Abstract

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5 The present invention relates to glycinamide derivatives of formula I, the
use of the compounds of formula I as inhibitors of raf-kinase, the use of
the compounds of formula I for the manufacture of a pharmaceutical
composition and a method of treatment, comprising administering said
pharmaceutical composition to a patient.

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